EVALUATION OF DIETARY FACTORS ASSOCIATED WITH SPONTANEOUS PANCREATITIS IN DOGS

A Thesis

by

KRISTINA YVONNE LEM

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

August 2007

Major Subject: Epidemiology

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Approved by:

Chair of Committee, Geoffrey T. Fosgate
Committee Members, Bo Norby
Jörg M. Steiner
Head of Department, Evelyn Tiffany-Castiglioni

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ABSTRACT

Evaluation of Dietary Factors Associated with Spontaneous Pancreatitis in Dogs.

(August 2007)

Kristina Yvonne Lem, B.S., The University of Texas at Austin;

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Chair of Advisory Committee: Dr. Geoffrey T. Fosgate

This study estimates the association between dietary factors and spontaneous pancreatitis in dogs. A case-control study was conducted using 198 dogs with a clinical diagnosis of pancreatitis and 187 control dogs with a diagnosis of renal failure without clinical evidence of pancreatitis. Information on signalment, weight, body condition, dietary intake, medical history, diagnostic tests performed, concurrent diseases, treatment, length of hospital stay, and discharge status was extracted from medical records for dogs admitted to the Texas A&M University Small Animal Clinic (TAMU SAC) during January 2000 to December 2005. Information on dietary intake, signalment, weight, medical, surgical and environmental history was collected for the same dogs through a telephone questionnaire conducted from November 2006 through January 2007. Descriptive statistics were calculated, tabular analyses performed, and logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

Based on information extracted from the medical records, ingesting unusual food (OR=4.3; CI=1.7 to 10.7), ingesting table food (OR=1.5; CI=1.0 to 2.2), or exposure to both of these dietary factors (OR=2.1; CI=1.3 to 3.2) increased the odds of pancreatitis.

Collected through the telephone questionnaire, ingesting unusual food (OR=6.1; CI=2.2 to 16.5), ingesting table scraps the week before diagnosis (OR=2.2; CI=1.2 to 3.8) or regularly throughout life (OR=2.2; CI=1.2 to 4.0), and getting into the trash (OR=13.2; CI=2.1 to undefined) increased the odds of pancreatitis. Multivariable modeling estimated the associations of exposure to one or more dietary factors reported through the telephone questionnaire (OR=2.6; CI=1.4 to 5.0), overweight (OR=1.3; CI=0.7 to 2.5), year of diagnosis (OR=3.5; CI=1.9 to 6.5), neuter status (OR=3.6; CI=1.4 to 9.5), non-neuter surgery (OR=21.1; CI=3.3 to 133.9) and an interaction term between neuter status and non-neuter surgery (OR=0.1; CI=0.01 to 0.4). Dietary factors increase the odds of spontaneous pancreatitis in dogs.

I dedicate this thesis to my loving husband, Steve. He has been an unending source of support, encouragement, hugs and jokes. He has supported my decisions, encouraged me to keep on going, hugged me when I was tired, and told me jokes when I felt discouraged.

I also dedicate this thesis to the rest of my family who held me accountable. To my dad, Jim Foley, who asked "You're not done yet?" To my mom, Judi Prukop who supported me no matter what I did. To my sister, Debbi Kjällbring and her family Henrik and Lukas for providing a source of stress relief in the garden they put in my yard that I didn't have the time to do. To my aunt and uncle Pat and Donald Hlozek for being close by when I needed a home away from home. Thank you all for the support I needed to achieve my goals.

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I would like to acknowledge the ladies in the medical records office. They pulled over 700 medical records out of storage for me, without complaint. Thankfully, their patience even extended to when I asked them for the records for the third time. I would also like to thank those telephone questionnaire respondents who actually called me, wanting to participate in my study. Their eagerness to help decreased my stress level when attempting to contact everyone else.

Finally, I would like to acknowledge my fellow graduate students. Walid Alali, whose desk was next to mine, either had an answer for just about any question I threw at him or looked one up. Holli Tietjen, Brenda Jacklitsch, Brandon Dominguez, and Brie

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CHAPTER I

INTRODUCTION

Background

Pancreatitis occurs when digestive enzymes are prematurely activated within the pancreas. The claims that dietary indiscretion, including home cooked diets and table scraps, is a risk factor for spontaneous canine pancreatitis are based on anecdote, rather than empirical evidence.[1,2] A high fat diet has been shown to induce[3] and increase the severity[4] of experimental pancreatitis. For the purpose of this study, dietary factors evaluated included ingestion of food other than commercially prepared dog food or a special diet prepared according to a recipe prescribed by a veterinarian. Information on dietary factors extracted from the medical records included consumption of table food, and any food item that the dog did not regularly consume. Information on dietary factors included in the telephone questionnaire were the consumption of table scraps, any food item that the dog did not regularly consume, any food item out of the trash, and any food item given to the dog by someone other than the owner.

Pathophysiology

The pancreas is composed of both exocrine and endocrine tissue.[5,6,7] The endocrine tissue makes up only 1-2% of the pancreatic mass.[6,7] It is composed of Islets of Langerhans that contain four types of endocrine cells that synthesize and secrete

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This thesis follows the style of *Journal of the American Veterinary Medical Association.*

insulin, glucagon, pancreatic polypeptide, and somatostatin.[6,7] The exocrine tissue makes up approximately 98% of the pancreatic mass[6,7] and its major function is the synthesis and secretion of digestive enzymes and zymogens of these enzymes.[5] The microscopic lobules of the exocrine pancreas are composed of acinar cells and a branching duct system.[5] The acinar cells are the cells that synthesize digestive enzymes and store them in zymogen granules.[5] The branching duct system consists of intralobular ducts, interlobular ducts and the main pancreatic ducts that empty into the proximal duodenum.[5] The ductal epithelium synthesizes bicarbonate, which along with proteolytic enzymes is essential for normal food digestion.[8]

Zymogens are catalytically inactive forms of digestive enzymes produced in the acinar cells of the pancreas.[9] They include trypsinogen, chymotrypsinogen, kallikreinogen, proelastase, procarboxypeptidase, and prophospholipase A_2.[9] They are activated by the cleavage of their activation peptide, a small peptide at the amino-terminus of the polypeptide chain, once they have left the pancreas and have been released into the proximal small intestine.[9]

Zymogens and lysosomal enzymes are segregated into different granules at the Golgi apparatus of the acinar cell.[9] This prevents contact between zymogens and lysosomal enzymes, which could lead to premature activation of the zymogens. Trypsin, the active form of trypsinogen, plays a central role in activating all other zymogens.[8,10] This role played by trypsin is dependent on the calcium concentration, and pH of its immediate environment.[8,10] As calcium concentrations increase, the efficiency of trypsin-mediated cleavage of the trypsinogen activation peptide (TAP) also increases.[8]

Calcium binding to trypsin also protects against hydrolysis by other trypsin molecules.[8] Areas of low calcium concentration, such as in the pancreas, are protective of the trypsinogen activation peptide (TAP) against cleavage.[8] The secretion of bicarbonate by the ductal epithelium maintains an alkaline pH that also prevents autoactivation of zymogens.[8]

Pancreatic secretory trypsin inhibitor (PSTI) is synthesized, transported, and stored together with the zymogens and protects the pancreas by preventing prematurely activated trypsin from initiating the zymogen activation cascade within the acinar cell.[8,9] This trypsin inhibitor is believed to bind to the active site of trypsin in acinar cells and this prevents hydrolysis of more trypsinogen to trypsin and TAP, and thus further premature trypsinogen activation.[8,9] A muscle sphincter (sphincter of Oddi) prevents backward flow of activated enzymes into the pancreatic duct.[11] Serum protease-inhibitors, including α_1-proteinase inhibitor and α_2-macroglobulin, bind to trypsin in the blood, scavenging active trypsin and other proteases from the vascular space.[12] The α_2-macroglobulin irreversibly binds all endopeptidases in the blood and plays a central role in rapidly clearing them from the blood.[12] The main function of α_1-protease inhibitor is the inhibition of neutrophil elastase during inflammation.[13] It plays a minor role in reversibly binding serine proteinases including trypsin, chymotrypsin, and elastase.[12]

Once zymogens are secreted into the duodenum, they encounter enteropeptidase that is produced by the brush border cells of the duodenum.[11] Enteropeptidase is a protease that is 2000 times more effective than trypsin at activating trypsinogen.[11]

Activation of trypsinogen and other zymogens within the pancreas can cause cellular necrosis, endothelial damage, and increased capillary permeability. The increased capillary permeability can lead to pancreatic edema, decreased microvascular circulation, and local ischemia. Tissue destruction leads to further activation of trypsin increasing inflammation and causing more damage. The inflammatory response to pancreatic autodigestion can lead to systemic disease including hypovolemic shock, acute renal failure, acute lung failure, disseminated intravascular coagulopathy (DIC), multiple organ dysfunction syndrome (MODS), and death.[14,15]

When the normal protective mechanisms are overcome and zymogens are activated while still in the pancreas, damage to pancreatic tissue results.[9] Within the acinar cells, the fusion of lysosomes and zymogen granules can cause inappropriate zymogen activation. This occurs if there is a massive buildup of the zymogen granules within the pancreas and the vacuoles rupture.[9] The ruptured vacuoles cause a decrease in pH and release trypsin within the pancreas causing autodigestion, inflammation, and further zymogen activation.[9] Once trypsinogen is activated to trypsin, the activated trypsin furthers the cascade by activating more trypsinogen and other zymogen molecules.

Epidemiology

The causes of spontaneous canine pancreatitis are poorly understood. However, there are a number of risk factors that have been associated with this disease. Breeds such as Terriers and Miniature Schnauzers (OR=41.8) appear to have an increased risk,

while Labrador Retrievers (OR= 0.1) and Miniature Poodles (0.004) have a decreased risk.[1] The risk has also been shown to be higher in middle-age (OR= 27.5) to older dogs (OR= 36.9), overweight dogs (OR=2.9) , and dogs with concurrent endocrine diseases including diabetes mellitus (OR=36.5), hyperadrenocorticism (OR=4.3), and hypothyroidism (OR=10.7).[1,2]

Hyperlipidemia, including hypertriglyceridemia, hypercholesterolemia, and grossly visible serum lipemia, is seen in canine patients with spontaneous pancreatitis.[1,16,17] Severe hypertriglyceridemia, TG>902.5 mg/dl, has been shown to be a risk factor for pancreatitis in Miniature Schnauzers.[18] In contrast, hypercholesterolemia has not been shown to be associated with pancreatitis.[19]

Other factors that have been identified include prior gastrointestinal disease (OR= 168), hypercalcemia, epilepsy (OR= 17.1), and blunt abdominal trauma.[1,2] Other factors potentially associated with pancreatitis include drugs, anesthesia, and surgery.[2] Seasonality has not been shown to be associated with development of fatal acute pancreatitis.[1] However, more food is often available around holidays with more people present to offer food to dogs. This greater availability can increase the chances of a dog to be exposed to food that could increase the risk of pancreatitis. However, such an association has not yet been demonstrated.

A clinically useful classification system for spontaneous canine pancreatitis has not been standardized in veterinary medicine.[20] As a result, similar terms can have different meanings in different publications.[1,2] In human medicine, a standard clinically based classification system for acute pancreatitis has been developed.[21] According to

this classification system, acute pancreatitis is defined as pancreatic inflammation with the inflammation being reversible once the causal factor has been removed.[22] Acute pancreatitis can be either mild or severe.[20,21] Mild acute pancreatitis is defined as having a limited amount of local or distant complications without multisystem failure and an uncomplicated recovery.[21,22] Severe acute pancreatitis is associated with systemic complications and often leads to multiple organ failure.[16,21,22] Multiple organ failure can include hypotensive shock, acute renal failure, disseminated intravascular coagulopathy (DIC), lung failure, and can lead to death.[14,15] Chronic pancreatitis is defined as long-term inflammation of the pancreas with irreversible morphologic changes, including fibrosis and atrophy.[20,22] Pancreatic complications that can occur in conjunction with acute or chronic pancreatitis include acute fluid collections, pancreatic necrosis, acute pseudocysts, and pancreatic abscess.[21,22] Histopathologic examination is required to definitively distinguish acute and chronic pancreatitis.[21]

Clinical, clinicochemical, and imaging signs of pancreatitis

Pancreatic inflammation has both local and systemic effects and the severity of the inflammation determines observable clinical signs. Mild inflammation can result in either subclinical disease or only mild clinical signs. More severe inflammation can result in a variety of clinical signs. Those signs may include anorexia, vomiting, abdominal pain, and diarrhea.[1,23] Systemic clinical signs can include fever, dehydration, weakness, respiratory distress, and cardiovascular shock.[23,24] Although these clinical

signs are not specific to pancreatitis, any dog with vomiting and cranial abdominal pain should be evaluated for pancreatitis.[24]

It is believed that the majority of canine pancreatitis cases are not recognized by veterinarians and therefore the true incidence is unknown.[24] Clinical diagnosis is often difficult because the majority of clinical signs are non-specific, and diagnostic testing has traditionally been considered unreliable.[23,24] Historically, serum lipase activity had been measured to evaluate pancreatic function and used as a diagnostic test for pancreatitis.[25] Because some dogs with pancreatitis do not demonstrate an increase in serum lipase activity,[25] and because there are sources of lipase activity in the body other than the pancreas,[26] serum lipase activity is neither sensitive nor specific for pancreatitis.[27,28] The serum lipase and amylase activity have been shown to have a sensitivity of 51.7% and a specificity of 66.6%.[29]

Radiologic and ultrasonographic findings are subjective, and the diagnostic accuracy of abdominal ultrasound is heavily dependent upon the skill of the operator. However, despite the degree of subjectivity, abdominal ultrasound has been shown to have a sensitivity of 68%,[23] and can be a useful tool in the diagnosis of pancreatitis. Canine pancreatic lipase immunoreactivity (cPLI) concentration exclusively measures the serum concentration of lipase that originates from the exocrine pancreas.[30] The specificity of cPLI has not been reported, however, when tested in dogs with Exocrine Pancreatic Insufficiency, when pancreatic lipase is known to be low, all dogs in the study had cPLI values below the reference range.[31] This high level of specificity of cPLI

for the exocrine pancreas, and a sensitivity of 82%[30] make it the most sensitive and specific test currently available for canine pancreatitis.

Objective

The primary objective of this retrospective case-control study was to determine if dietary factors predispose dogs to spontaneous pancreatitis. Information retrieved from medical records and a telephone questionnaire compared the food intake of a case group of dogs diagnosed with pancreatitis with a similarly sized control group of dogs diagnosed with renal failure at the Small Animal Clinic at Texas A&M University (TAMU SAC) from January 1, 2000 through December 31, 2005. The secondary objective of this study was to identify non-dietary variables that were associated with pancreatitis within this study population.

CHAPTER II

EVALUATION OF A POSSIBLE ASSOCIATION OF DIETARY FACTORS WITH SPONTANEOUS PANCREATITIS IN DOGS

Introduction

Pancreatitis occurs when digestive enzymes are prematurely activated within the pancreas. The claims that dietary factors are risk factors for spontaneous canine pancreatitis are based on anecdote, and not empirical evidence.[1,2] However, a high fat diet has been shown to induce[3] and increase the severity[4] of experimental pancreatitis. Dietary factors assessed in this study include the consumption of any food that is not a commercially manufactured dog food, or based on a recipe prescribed by a veterinarian.

The pancreas is composed of 98% exocrine tissue,[6,7] which predominately synthesizes and secretes digestive enzymes and inactive pre-forms or zymogens.[5,9] The pancreas has a number of natural protective mechanisms that ensure the zymogens are not activated until they reach the duodenum.[5,8,9,10,11] Pancreatitis occurs when these natural mechanisms are overcome, and zymogens are prematurely activated.[9]

Pancreatic inflammation has both local and systemic effects and the severity of the inflammation determines the clinical signs observed. Mild inflammation can result in either subclinical disease or mild clinical signs. More severe inflammation can result in a variety of local and systemic effects, leading to clinical signs, such as anorexia, vomiting, weakness, abdominal pain, dehydration, and diarrhea.[1,23] Systemic clinical signs can include fever, respiratory distress, and cardiovascular shock.[23,24] Although

these clinical signs are non-specific, any dog with vomiting and cranial abdominal pain should be evaluated for pancreatitis.[24]

It is believed that the majority of canine pancreatitis cases are not recognized due to difficulty of diagnosis and therefore the true incidence is unknown.[24] Definitive diagnosis can be difficult because the majority of clinical signs are not specific for pancreatitis, and diagnostic testing has traditionally been considered unreliable.[23,24] Historically, serum lipase and amylase activities have been used as diagnostic tests for canine pancreatitis.[25] Because some dogs with pancreatitis do not demonstrate an increase in serum lipase activity,[25] and because there are sources of lipase in the body other than the pancreas,[26] serum lipase activity is neither sensitive nor specific for pancreatitis.[27,28] The serum lipase and amylase activity have been shown to have a sensitivity of 51.7% and a specificity of 66.6%.[29]

Abdominal ultrasound has been shown to have a sensitivity of 68%,[23] and can be a useful tool in the diagnosis of pancreatitis. Canine pancreatic lipase immunoreactivity (cPLI) measures the serum concentration of lipase of exocrine pancreatic origin.[30] The specificity of cPLI has not been reported, however, when tested in dogs with Exocrine Pancreatic Insufficiency (pancreatic lipase known to be low) all dogs in the study had cPLI values below the reference range.[31] This high level of specificity of cPLI for the pancreas, and a sensitivity of 82%[30] make it the most sensitive and specific test currently available for the diagnosis of canine pancreatitis.

Pancreatitis affects dogs of all ages and body conditions, as do many other diseases. Potential risk factors have been evaluated for acute,[2] and fatal acute[1] spontaneous pancreatitis in an attempt to increase our understanding of this disease.

Dietary factors associated with spontaneous pancreatitis in dogs have not been previously evaluated. However, it has been noted that the onset of clinical signs of pancreatitis in some patients can follow ingestion of fatty food.[23] Dietary factors are commonly accepted as risk factors. However, when risk factors for spontaneous canine pancreatitis have been evaluated, dietary factors have been excluded from analysis.[1]

The primary objective of the study reported here was to determine if dietary factors are associated with an increased risk for spontaneous pancreatitis in dogs. The secondary objective was to identify other non-dietary factors that were associated with an increased risk for pancreatitis. The study included extraction of data from medical records, and conducting a telephone questionnaire. To achieve these objectives, a retrospective case-control study was performed based on records from the Small Animal Clinic at Texas A&M University (TAMU SAC) during the period from 2000 to 2005.

Materials and Methods

All protocols were reviewed and approved by the Institutional Review Board at Texas A&M University.

Case definition and selection—An affected dog was defined as any dog admitted to the TAMU SAC that had a complete medical record and met the inclusion criteria. A case dog was an individual dog with a record in the patient-record database

that described the first in-patient visit during the period from January 1, 2000 through December 31, 2005 that had the diagnostic code “pancreatitis” (code:690010000). Diagnostic criteria were at the discretion of the clinician who saw the dog and included one or more of the following: clinical signs, radiology, ultrasonography, serum cPLI concentration, and histopathology. Subsequent visits of the same patient with any diagnosis of pancreatitis, and outpatient records were excluded. Patients with a concurrent illness that was the primary reason for presentation were also excluded. These included acute or chronic renal failure unrelated to pancreatitis, acute or severe intervertebral disk disease, trauma secondary to being hit by a car, esophageal foreign body, seizures, and malignant neoplasia.

Definition and selection of control population—A control dog was defined as any dog that was admitted and diagnosed with acute or chronic renal failure at TAMU SAC during the same time period as the cases. A control dog was an individual dog with a record in the patient-record database that described a first-time inpatient visit from January 1, 2000 through December 31, 2005 that had the diagnostic description “kidney failure due to unknown” (code: 7100Y000X). Controls were frequency matched to cases based on a proxy for severity of disease.

Control dogs with a concurrent diagnosis of pancreatitis, acute or severe intervertebral disk disease, trauma secondary to being hit by a car, esophageal foreign body, seizures, and malignant neoplasia were excluded. Control dogs with a prior diagnosis of pancreatitis during any time point of its life that had resolved but did not have pancreatitis as a concurrent diagnosis were retained in the control group.

The disease severity categories for pancreatitis and renal failure were defined as: not treated with intravenous (IV) fluids and discharged from the hospital alive, treated with IV fluids and discharged from the hospital alive, or died or euthanized while in the hospital. When a disease severity category had more control dogs than case dogs, control dogs were randomly selected to equal the number of case dogs for each category. All control dogs were selected from a disease severity category when the category had more case dogs than control dogs.

Primary exposure variables of interest—Dietary factors were extracted from the medical record and a telephone questionnaire. Three direct measures were extracted from the medical record when available: ingestion of any table food on a regular basis other than a veterinary prescribed homemade diet, ingestion of food items that were unusual for the dog, ingestion of either or both table food and an unusual food item. Proximity to a holiday was also evaluated based on the recorded date of admission.

The holidays evaluated were New Year's Day, Fat Tuesday, Easter, Memorial Day, Independence Day, Labor Day, Halloween, Thanksgiving, and Christmas. A time frame of seven days following the holidays was included for each holiday except for Easter, Thanksgiving, and Christmas. Because food preparations typically begin before these three holidays, the holiday itself as well as the following seven days was included.

Six dietary factors were recorded from the telephone questionnaire: ingestion of an unusual food item during the week before admission to the TAMU SAC, ingestion of table scraps during the week before admission, routine ingestion of table scraps, ingestion of food items from the trash during the week before admission, presence at a

large gathering with food during the week before admission, and any combination of the first five categories were included in the analysis. Ingestion of non-food items including owner medications, ethylene glycol, stuffed toys, and gloves were excluded from the definition.

Data from medical records—Medical records of all dogs were reviewed for age at diagnosis in years, breed, sex, discharge status of the dog, the number of days spent in the hospital, the number of days treated with intravenous (IV) fluids, and the date of admission to the TAMU SAC. Sexual status (neutered versus intact), body weight in pounds, body condition, concurrent diseases, diet, grossly visible serum lipemia, and canine pancreatic lipase immunoreactivity (cPLI) concentrations were extracted from the records as recorded on the day of admission to the TAMU SAC.

Body condition was categorized as underweight, normal, or overweight as determined by the body condition score (BCS) when available and comments recorded in the record when the body condition score was not available. Both the 5-point and 9-point BCS scales were found in the medical record. On a 5-point BCS scale, less than 2.5/5 was coded as underweight, 2.5-3.5/5 was coded normal, and greater than 3.5/5 was coded overweight. On a 9-point BCS scale, less than 4/9 was coded as underweight, 4-6/9 was coded as normal, and over 6/9 was coded as overweight. If a body condition score or specific comments were not recorded, then the dogs were assigned a classification based on the recorded weight as compared to the American Kennel Club (AKC) standard suggested value ranges. If the dog's body weight fell within the AKC body weight range, the dog was coded as normal. If the dog's body weight fell above or

below the AKC body weight range, the dog was coded as overweight, or underweight respectively. Discharge status was recorded as alive, euthanized, or died without euthanasia. Diet history was extracted from the general entrance questionnaire that clients complete while in the waiting room, and from the history sheet that senior veterinary students complete while questioning the owner in the examination room. Grossly visible lipemia was recorded as either positive or negative as stated on the hematology or serum chemistry profile from the clinical pathology service at TAMU. Dogs that were diagnosed with hypothyroidism during the visit of interest or were taking hypothyroid medication at the time of the visit were considered to have a concurrent diagnosis of hypothyroidism.

Telephone questionnaire— Owner addresses and telephone numbers were obtained from the medical record. A copy of the telephone questionnaire, a letter of introduction, and an information sheet about the study were mailed to the owners in batches of 100 each. The order of mailings was random based on case or control status to blind the investigator while conducting the questionnaire. Owners were called on the telephone starting one week after the mailings and asked to participate in the questionnaire. If they declined, the conversation was ended by thanking them for their time, and the owner was recorded as "declined". If they accepted, the questionnaire was conducted following the approved telephone script. If an answering machine picked up, a voice message was left. If the phone continued to ring, the call was discontinued after 10 rings. If a recording announced a disconnected number, the number was recorded as "disconnected". If a person claimed no knowledge of the dog, the number was recorded

as a "wrong number". Three attempts were made to contact each owner. The date and time of each attempt was recorded on the questionnaire. If an owner was not contacted by the third attempt, and an answering machine was reached, the owner was informed that no additional attempts for contact would be made but they were invited to call if they would like to participate in the questionnaire. A batch of 100 information packets was mailed out every 1-2 weeks during October 9, 2006 through November 21, 2006 until a packet had been sent to every owner of the dogs included in this study. The telephone questionnaire (Appendix B) included questions about the dog's signalment, health history, housing, preventative health treatments, and other pets in the household. Health history included questions about prescription medication, prior illnesses, prior traumatic events, and prior surgeries that were further categorized into neuter surgery, and invasive non-neuter and non-invasive non-neuter surgery. Invasive non-neuter surgery was defined as all surgeries that were invasive of the abdominal or pelvic cavities, or cancer removals. Non-neuter surgeries that were not considered invasive were all orthopedic surgeries, dentals, cosmetic surgeries, and benign lump or cyst removals. The owner was questioned on the dog's regular diet and the aforementioned dietary factors under investigation. Each questionnaire was concluded with the collection of demographic information of the owner.

Statistical analysis—Descriptive statistics were calculated for all variables. Continuous variables, including age, weight, days in the hospital, days on fluids, and serum cPLI concentrations, were summarized by the mean, median, interquartile range, standard deviation, and Kolmogorov-Smirnov test for normality. Mann-Whitney U tests

were performed for each variable to determine if there were significant differences in medians between cases and controls.

Categorical variables, including sex, sexual status, grossly visible serum lipemia, hypothyroidism, hyperadrenocorticism, diabetes mellitus, referral status, proximity to a holiday, breed, year of diagnosis, overweight status, and dietary factors were compared based on case/control status using frequency tables and the chi-square test. When the assumption of the chi-square test was not met, and fewer than 80% of the cells had an expected frequency greater than or equal to 5, the Fisher exact test was used. The crude odds ratio, 95% confidence interval, and Pearson chi-square P value were calculated in non-stratified analyses. The adjusted odds ratio, 95% confidence interval, and Mantel-Haenszel chi-square P value were calculated when the variables were stratified based on the severity of disease matching factor.

Binary logistic regression was used to estimate the association between case/control status, whether or not the dog was diagnosed with pancreatitis, and the variables under study. Bivariable analysis was used to evaluate each variable individually with case/control status. A P value less than or equal to 0.2 was considered significant in the screening bivariable models. The primary exposure of interest was any inappropriate dietary ingestion as reported during the telephone questionnaire. The odds ratio (OR) of the primary exposure from bivariable analysis (crude OR) was compared with the OR for the primary exposure when evaluated with each variable individually from bivariable analysis (adjusted OR). Those variables with a 15% or more difference between the adjusted odds ratio and crude odds ratio were considered confounders.

Presence of effect modification was evaluated by including interaction terms in the model.

Multivariable analysis included confounders and those variables that were found to be statistically significant based on the bivariable analysis as a starting point for model building. Any inappropriate dietary factor as measured from the telephone questionnaire was the primary variable of interest. The model building included the data on the 114 cases and 113 controls from the telephone questionnaire respondents exclusively. The rest of the dogs, from the medical records, were considered missing because they did not have telephone questionnaire data. The primary exposure, and all variables determined to be confounders were forced into the model. Backward stepwise analysis based on conditional likelihood ratio tests was used to determine the final main effects only model. All pairwise interaction terms in the main effects model were created and tested for significance using a backward stepwise analysis. Variables that demonstrated effect modification based on the initial stratified analysis were added into the model, as well as the interaction term between the variable and the main effects variable. These terms were assessed for significance within the model using binary logistic regression according the Wald P value. Odds ratios and 95% confidence intervals were estimated.

Variables extracted from the medical records were compared between responders and non-responders to the telephone questionnaire. Medians of continuous variables were compared using Mann-Whitney U tests, and the proportions of the categorical variables were compared using Pearson chi-square tests. All statistical analyses were

performed using a commercially available software package[a] and interpreted at the 5% level of significance. An exact software package[b] was used when there were contingency tables with zero cell totals in the bivariable analysis.

Results

From January 1, 2000 to December 31, 2005, 265 dogs were diagnosed with pancreatitis at TAMU SAC and 472 dogs were diagnosed with renal failure. Of those 737 dogs, 198 met the inclusion criteria for the case group, and 186 met the inclusion criteria for the control group. There was a 59% response proportion for the telephone questionnaire with 114 respondents being owners of dogs diagnosed with pancreatitis and 113 respondents being owners of dogs diagnosed with renal failure.

The continuous variables age, weight, days in the hospital, days on IV fluids, and serum cPLI concentrations were not normally distributed based on the Kolmogorov-Smirnov test. The medians for age (P=0.105), weight (P=0.002), days in the hospital (P=0.003), and days on IV fluids (P=0.004) were significantly different between the case and control group at the 0.2 level for evaluation in the multivariable model (Table 1). Days in the hospital, and days on IV fluids were not evaluated in the multivariable model because those variables were used to assess severity, which was the matching criterion of controls to cases. Serum cPLI concentration was not significantly different between the case group and the control group. The control group result was based on three data points. Because neither the case definition nor the exclusion criteria included the results

[a] SPSS version 12.0.1 for Windows, SPSS Inc., Chicago, IL
[b] LogXact.7, Cytel Inc., Cambridge, MA

of serum cPLI concentration, the control dog with a serum cPLI concentration reading above 200 µg/L was not excluded from the control group.

Adjusted ORs stratified on the matching factor, severity of disease, 95% CI and Mantel-Haenszel 2-sided P values and crude (unadjusted) ORs, 95% CI and Pearson 2-sided P values were calculated for each potential risk factor. When there was no evidence of confounding by the matching variable, the crude ORs were reported for their higher precision. Odds of pancreatitis in neutered dogs were 2.7 (CI=1.7 to 4.5; P=0.0005) times higher than in intact dogs, and castrated males had a 2.0 (CI=1.3 to 3.1; P=0.002) times higher odds of pancreatitis than all other dogs (Table 2).

Table 1. Descriptive statistics and comparison of continuous variables in 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical records.

	Cases (pancreatitis)			Controls (renal failure)			Mann-Whitney
Variable	**Median (Mean)**	**Interquartile range**	**Standard deviation**	**Median (Mean)**	**Interquartile range**	**Standard deviation**	**P value**
Age (years)	8.00 (7.88)	6.0	3.81	7.00 (7.23)	7.0	4.27	0.105
Weight (lbs)	20.00 (30.52)	34	24.65	32.65 (39.38)	45.0	29.23	0.002
Hospital stay(days)	3.00 (3.97)	5.0	4.30	1.00 (2.93)	4.0	3.70	0.003
IV fluids (days)	2.00 (2.46)	4.0	2.58	0.50 (1.86)	3.0	2.86	0.004
Serum cPLI (µg/L)	333.00 (362.06)	389.5	276.07	148.30 (203.37)	194.2	108.18	0.328

Table 2. Comparison of sex and sexual status between 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the time period of 2000 to 2005. Data were extracted from the medical records.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Sex; n=384			1.1 (0.7, 1.6)	0.674
Male	188	99		
Female	196	99		
Sexual status; n=384			2.7 (1.7, 4.5)	0.00005
Neutered	293	168		
Intact	91	30		
Castrated male; n=384			2.0 (1.3, 3.2)	0.002
Yes	127	80		
No	257	118		
Sex and sexual status; n=384				0.0002
Spayed female	166	88	1.0 (referent)	
Intact female	30	11	0.5 (0.2, 1.2)	
Castrated male	127	80	1.5 (0.9, 2.5)	
Intact male	61	19	0.4 (0.2, 0.8)	
Spayed female; n=384			1.1 (0.7, 1.7)	0.620
Yes	166	88		
No	218	110		

*P value based on Pearson chi-square test

Neither sex had higher odds of pancreatitis than the other (Table 2). Of the multicategorical variables, there was a significant difference between the pancreatitis and renal failure dogs based on American Kennel Club group (P=0.001), with the terrier group having the most case dogs, 44 out of 64 total, followed by the toy group, 41 out of 70 (Table 3). Breeds with more than 5 dogs diagnosed with pancreatitis, (P=0.001) were significantly different between pancreatitis and renal failure dogs (Table 3). Odds of pancreatitis were 4.1 (CI=1.9 to 9.2; P=0.0002) times greater in Miniature Schnauzers, 4.3 (CI=1.2 to 15.3; P=0.015) times greater in Yorkshire Terriers, and 2.5 (CI=1.4 to 4.5; P=0.001) times greater in the Terrier group (Table 4).

Dogs with grossly visible lipemic serum had a 3.9 (CI=1.9 to 8.1; P=0.0001) times higher odds, and those with diabetes mellitus had a 3.6 (CI=1.0 to 13.1; P=0.039) times higher odds of pancreatitis than those dogs without (Table 5). Dogs that were current on their annual vaccinations had a 3.7 (CI=0.8 to 18.2; P=0.086) times higher odds of pancreatitis than dogs that were not current (Table 6). Dogs that had undergone

surgery at any time prior to diagnosis of pancreatitis or renal failure had 7.2 (CI=2.9 to 18.0; P=0.000007) times higher odds of pancreatitis than those dogs that had not undergone prior surgery (Table 7). The type of surgery performed on intact dogs showed an association with invasive surgery increasing the odds of pancreatitis 27.5 (CI=3.5 to undefined) times, and non-invasive surgery increasing the odds of pancreatitis 4.0 (CI=0.2 to 61.6) times more than intact dogs that did not undergo prior surgery. Prior non-neuter surgery did not increase the odds of pancreatitis among neutered dogs. Dogs that had suffered prior trauma did not have higher odds of pancreatitis (Table 7). The incidence of pancreatitis per year during the period of 2004 to 2005 was higher (OR=1.8; CI=1.2 to 2.8; P=0.004) than for the period of 2000 to 2003 (Table 8). Dogs did not have an increased odds of pancreatitis around the holidays (OR=0.7, CI=0.4 to 1.2; P=0.176; Table 8). Overweight dogs had a 1.9 times higher odds of pancreatitis than dogs that were normal or underweight (Table 8).

Table 3. Comparison of groups of dog breeds of 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical records.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
AKC group; n=384				0.001
Herding	38	14	0.6 (0.2, 1.6)	
Hound	26	15	1.4 (0.4, 4.2)	
Mixed	60	34	1.3 (0.5, 3.2)	
Non-sporting	38	19	1.0 (referent)	
Sporting	71	26	0.6 (0.2, 1.4)	
Terrier	63	44	2.3 (0.9, 5.8)	
Toy	70	41	1.4 (0.6, 3.4)	
Working	18	5	0.4 (0.1, 1.5)	
Breeds; n=384				0.001
Dachshund	18	11	1.8 (0.6, 5.3)	
Golden Retriever	13	7	1.3 (0.4, 4.6)	
Labrador Retriever	23	8	0.6 (0.2, 1.6)	
Miniature Schnauzer	39	31	4.4 (1.9, 10.9)	
Toy Poodle	11	5	1.0 (0.3, 3.6)	
Yorkshire Terrier	16	13	5.0 (1.3, 22.5)	
Other	264	123	1.0 (referent)	

*P value based on Pearson chi-square test

Table 4. Comparison of breeds of 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical record.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Miniature Schnauzer; n=384			4.1 (1.9, 9.2)	0.0002
Yes	39	31		
No	345	167		
Yorkshire Terrier; n=384			4.3 (1.2, 15.3)	0.015
Yes	16	13		
No	368	185		
Labrador Retriever; n=384			0.5 (0.2, 1.2)	0.097
Yes	23	8		
No	361	190		
Miniature Poodle; n=384			0.9 (0.2, 4.7)	0.938
Yes	6	3		
No	378	195		
Terrier group; n=384			2.5 (1.4, 4.5)	0.001
Yes	63	44		
No	321	154		

P value based on Pearson chi-square test

Table 5. Comparison of concurrent illnesses of 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during 2000 to 2005. Data were extracted from the medical record.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Grossly visible lipemic serum; n=384			3.9 (1.9, 8.1)	0.0001
Yes	46	36		
No	338	162		
Hypothyroidism; n=384			1.0 (0.5, 2.0)	0.987
Yes	35	18		
No	349	180		
Hyperadrenocorticism; n=384			1.5 (0.5, 4.8)	0.464
Yes	13	8		
No	371	190		
Diabetes mellitus; n=384			3.6 (1.0, 13.1)	0.039
Yes	14	11		
No	370	187		

*P value based on Pearson chi-square test

Table 6. Comparison of prior illnesses and preventative care between 114 case dogs diagnosed with pancreatitis and 113 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were collected through a telephone questionnaire.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Prior illness; n=223			1.4 (0.8, 2.4)	0.197
Yes	98	54		
No	125	58		
Prescription medications; n=221			1.3 (0.7, 2.3)	0.447
Yes	64	35		
No	157	77		
Vaccination status; n=223			3.7 (0.8, 18.2)	0.086
Current	214	110		
Not current	9	2		
Heartworm prevention; n=222			1.0 (0.3, 3.3)	0.974
Yes	210	106		
No	12	6		

*P value based on Pearson chi-square test

Table 7. Comparison of prior trauma and surgery in 114 dogs diagnosed with pancreatitis and 113 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were collected through a telephone questionnaire.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Prior trauma; n=223			0.7 (0.4, 1.5)	0.362
Yes	39	17		
No	184	95		
Prior surgery; n=223			7.2 (2.9, 18.0)	0.000007
Yes	185	106		
No	38	6		
Non-neuter surgery; n=223			1.9 (1.1, 3.4)	0.032
Yes	67	41		
No	156	71		
Non-neuter surgery among intact dogs; n=45			16.0 (2.8, 92.7)†	0.002†
Yes	10	8		
No	35	7		
Non-neuter surgery among intact dogs; n=45				0.0005
Invasive surgery	6	6	27.5 (3.5, undefined)	
Non-invasive surgery	4	2	4.0 (0.2, 61.6)	
No surgery	35	7	1.0 (referent)	

Table 7. Continued

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Non-neuter surgery among neutered dogs; n=178			1.2 (0.7, 2.3)	0.532
Yes	57	33		
No	121	64		
Non-neuter surgery among neutered dogs; n=178				0.768
Invasive surgery	23	14	1.4 (0.5, 3.8)	
Non-invasive surgery	34	19	1.1 (0.5, 2.6)	
No Surgery	121	64	1.0 (referent)	

*P value based on Pearson chi-square test; †Adjusted (for matching factor) odds ratio, confidence interval, and Mantel-Haenszel P value are reported.

Table 8. Comparison of year of diagnosis, proximity to a holiday, and body condition in 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical records.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Year of diagnosis; n=384				0.011
2000	57	32	1.0 (referent)	
2001	57	23	0.5 (0.2, 1.2)	
2002	56	25	0.6 (0.3, 1.4)	
2003	55	22	0.5 (0.2, 1.2)	
2004	86	47	0.9 (0.5, 2.0)	
2005	73	49	1.6 (0.7, 3.5)	
Year of diagnosis (binary); n=384			1.8 (1.2, 2.8)	0.004
2004, 2005	159	96		
2000-2003	225	102		
Proximity of day of diagnosis to a holiday; n=384			0.7 (0.4, 1.2)	0.176
Yes	68	30		
No	316	168		
Body condition; n=348				0.011
Underweight	68	27	0.7 (0.4, 1.3)	
Normal weight	159	73	1.0 (referent)	
Overweight	121	73	1.8 (1.1, 3.0)	

Table 8. Continued

Variable		No. dogs	No. cases	OR (95% CI)	P value*
Overweight; n=348				1.9 (1.2, 3.0)	0.004
	Yes	121	73		
	No	227	100		

*P value based on Pearson chi-square test

Table 9. Comparison of dietary factors extracted from the medical records in 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005.

Variable		No. dogs	No. cases	OR (95% CI)	P value*
Unusual ingestion; n=348				4.3 (1.7, 10.9)	0.001
	Yes	32	26		
	No	316	159		
Table food; n=348				1.5 (1.0, 2.2)	0.082
	Yes	188	108		
	No	160	77		
Any inappropriate dietary factor; n=348				2.1 (1.3, 3.2)	0.001
	Yes	203	123		
	No	145	62		

*P value based on Pearson chi-square test

Dietary factors extracted from the medical records, or recorded through the telephone questionnaire were all associated with an increased odds of pancreatitis. An unusual ingestion as determined from the medical record, which included ingestion of any food item that the dog did not normally eat, increased the odds of pancreatitis 4.3 (CI=1.7 to 10.7; P=0.001) times, table food ingestion increased the odds 1.5 (CI=1.0 to 2.2; P=0.082) times, and either of the above (any inappropriate ingestion) increased the odds of pancreatitis 2.1 (CI=1.3 to 3.2; P=0.001) times over dogs that did not have these exposures (Table 9). When recorded through the telephone questionnaire, an unusual ingestion, which included ingestion of any food item that the dog did not normally eat, during the week before diagnosis at TAMU SAC increased the odds of pancreatitis 6.1 (CI=2.2 to 16.5; P=0.0001) times, ingestion of table scraps the week before diagnosis at TAMU SAC increased the odds 2.2 (CI=1.2 to 3.8; P=0.008) times, ingestion of table scraps regularly throughout life increased the odds 2.2 (CI=1.2 to 4.0; P=0.007) times, getting into the trash the week before diagnosis at TAMU SAC increased the odds 13.2 (CI=2.1 to undefined due to zero cell totals; P=0.003) times, being present at a family party with food and guests the week before diagnosis at TAMU SAC increased the odds of pancreatitis 3.6 (CI=0.7 to 17.9; P=0.09) times, and exposure to one or more of the five measures collected through the telephone questionnaire (any inappropriate dietary factor) increased the odds of pancreatitis 2.9 (CI=1.7 to 5.0; P=0.0001) times over dogs that were not exposed to these dietary factors (Table 10). There was an increasing odds of pancreatitis as the number of dietary factors the dog was exposed to increased.

Table 10. Comparison of dietary factors collected from the telephone questionnaire in 114 dogs diagnosed with pancreatitis and 113 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Unusual ingestion; n=227			6.1 (2.2, 16.5)	0.0001
Yes	30	25		
No	197	89		
Table scraps the week before diagnosis; n=227			2.2 (1.2, 3.8)	0.008
Yes	73	46		
No	154	68		
Table scraps throughout life; n=227			2.2 (1.2, 4.0)	0.007
Yes	69	44		
No	158	70		
Getting into the trash the week before diagnosis; n=227			13.2 (2.1, undefined)	0.003
Yes	9	9		
No	218	105		
Family party the week before diagnosis; n=227			3.6 (0.7, 17.9)	0.092
Yes	9	7		
No	218	107		
Any inappropriate dietary factor; n=227			2.9 (1.7, 5.0)	0.0001
Yes	97	63		
No	130	51		

Table 10. Continued

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Any inappropriate dietary factor; n=227				0.0004
No factors	131	52	1.0 (referent)	
1 factor	26	15	2.1 (0.8, 5.3)	
2 factors	53	32	2.3 (1.2, 4.7)	
3-5 factors	17	15	11.4 (2.5, 105.3)	

*P value based on Pearson chi-square test

Table 11. Comparison of other pets and housing in 114 dogs diagnosed with pancreatitis and 113 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were collected through a telephone questionnaire.

Variable	No. dogs	No. cases	OR (95% CI)	P value*
Other pets; n=223			1.2 (0.7, 2.1)	0.628
Yes	158	81		
No	65	31		
Housing; n=224				0.098
Inside	167	90	1.4 (0.7, 3.0)	
Outside	15	4	0.4 (0.1, 1.9)	
Both inside and outside equally	42	19	1.0 (referent)	

*P value based on Pearson chi-square test

Other pets in the household, and the dog's housing did not increase the odds of pancreatitis (Table 11). None of the owner demographic categories were associated with pancreatitis (Table 12). The "other" category for owner's race included 2 Hispanic, 1 Asian and 1African-American owner of dogs diagnosed with pancreatitis, and 4 Hispanic, 1 Asian and 1 African-American owner of renal failure dogs (Table 12).

Table 12. Comparison of owner demographics in 114 dogs diagnosed with pancreatitis and 113 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were collected through a telephone questionnaire.

Variable	No. dogs	No. cases	P value*
Owner's sex; n=218			0.232
Male	52	30	
Female	166	80	
Owner's race (binary); n=216			0.533†
Caucasian	206	106	
Other	10	4	
Owner's annual income; n=180			0.692
Up to $20,000	7	4	
$20,001 to $40, 000	15	8	
$40,001 to $70, 000	38	23	
$70,001 to $100, 000	36	19	
Above $100, 000	84	39	

Table 12. Continued

Variable	No. dogs	No. cases	P value*
Owner's education; n=214			0.673
Some high school	2	2	
High school diploma or GED	19	10	
Some college	45	25	
Bachelor's degree	82	41	
Master's degree	47	21	
Doctorate	19	9	

*P value based on Pearson chi-square test

†Fisher exact P value

The multivariable logistic regression model included any inappropriate dietary factor as reported in the telephone questionnaire as the primary exposure of interest. Only the variable overweight changed the odds ratio between the primary exposure and the outcome (case/control status) by 15% or more (16%) and was retained in the model to control for confounding. The final model included the primary dietary exposure (any inappropriate dietary factor), overweight, year of diagnosis as a binary variable (2000-2003 versus 2004-2005), non-neuter surgery, which was any surgery excluding neuter performed prior to the current visit, sexual status and an interaction term between sexual status and non-neuter surgery. The model was a good fit for the data based on the Hosmer and Lemeshow test with 8 df (χ^2=4.451; P=0.814).

Table 13. Multivariable logistic regression model for the estimation of measures of association between variables and spontaneous pancreatitis in 100 dogs diagnosed with pancreatitis and 105 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005.

Variable	**Parameter estimate ($\hat{\beta}$)**	**P value (Wald)**	**Odds ratio (95% CI)**
Any inappropriate dietary factor	0.95	0.004	2.6 (1.4, 5.0)
Overweight	0.24	0.480	1.3 (0.7, 2.5)
Year of diagnosis (dichotomized)	1.2	0.0001	3.5 (1.9, 6.5)
Non-neuter surgery	3.1	0.001	21.1 (3.3, 133.9)
Sexual status	1.3	0.009	3.6 (1.4, 9.5)
Neuter by non-neuter surgery interaction	-3.0	0.004	0.05 (0.01, 0.38)

$\text{LogOdds(pancreatitis)}=\beta_1(\text{diet}) + \beta_2(\text{overweight}) + \beta_3(\text{year}) + \beta_4(\text{surgery}) + \beta_5(\text{neuter}) + \beta_6(\text{neuter*surgery}) + \beta_0$

Results of the multivariable logistic regression analysis are reported as odds ratios, their corresponding 95% CI, and P values (Table 13). The effect of each variable is adjusted for the effects of all other variables in the model. Dogs that were exposed to any type of an inappropriate dietary factor as reported during the telephone questionnaire

had a 2.6 (CI=1.4 to 5.0; P=0.004) times higher odds of pancreatitis than those dogs that did not have any exposure. Dogs that visited the hospital during the period of 2004 to 2005 had a 3.5 (CI=1.9 to 6.5; P=0.0001) times higher odds of pancreatitis than dogs that visited the hospital during the period of 2000 to 2003. Within dogs that were intact, those that underwent non-neuter surgery at any time prior to disease diagnosis had a 21.1 (CI=3.3 to 133.9; P=0.001) times higher odds of pancreatitis than dogs that had never undergone surgery. Within the dogs that were neutered, those that underwent a non-neuter surgery at any time prior to disease diagnosis (OR=1.1; CI=0.52 to 2.2; P=0.844) did not have an increased odds of pancreatitis. Within dogs that did not have any other surgery, those that were neutered had a 3.6 (CI=1.4 to 9.5; P=0.009) times higher odds of pancreatitis than dogs that were intact. Within dogs that had non-neuter surgery at any time prior to disease diagnosis, those that were neutered had a 5.4 (OR=0.19; CI=0.03 to 1.1; P=0.060) times lower odds of pancreatitis compared to dogs that were intact.

Median days in the hospital, days on IV fluids, and serum cPLI concentrations were not significantly different between responders and non-responders to the telephone questionnaire (Table 14). However, median age and weight were different between the two groups.

Table 14. Descriptive statistics and comparison of continuous variables between 227 responders and 157 non-responders to a telephone questionnaire including 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical records.

	Responders to telephone questionnaire n=227			**Non-responders to telephone questionnaire n=157**			**Mann-Whitney U test**
Variable	**Median (Mean)**	**Interquartile range**	**Standard deviation**	**Median (Mean)**	**Interquartile range**	**Standard deviation**	**P value**
Age (years)	8.00 (7.97)	6.0	3.80	7.00 (6.98)	7.0	4.33	0.017
Weight (lbs)	26.60 (36.95)	41.0	27.27	22.40 (31.74)	34.0	27.14	0.047
Hospital stay (days)	2.00 (3.41)	5.0	3.91	2.00 (3.55)	5.0	4.26	0.685
IV fluids (days)	1.00 (2.22)	4.0	2.95	1.25 (2.11)	3.0	2.40	0.704
Serum cPLI (µg/L)	351.60 (363.21)	374.4	254.99	232.00 (346.51)	402.1	305.77	0.429

Table 15. Comparison of breeds between 227 responders and 157 non-responders of a telephone questionnaire including 198 pancreatitis dogs and 186 renal failure dogs from the TAMU SAC during the period of 2000 to 2005. Data were extracted from the medical records.

Variable	No. dogs	No. responders	P value*
AKC group; n=384			0.479
Herding	38	27	
Hound	26	15	
Mixed	60	33	
Non-sporting	38	25	
Sporting	71	41	
Terrier	63	38	
Toy	70	41	
Working	18	7	
Breeds; n=384			0.980
Dachshund	18	9	
Golden Retriever	13	7	
Labrador Retriever	23	14	
Miniature Schnauzer	39	22	
Toy Poodle	11	7	
Yorkshire Terrier	16	10	
Other	264	158	

*P value based on Pearson chi-square test

The multi-categorical variables, American Kennel Club group, breeds with five or more case dogs, body condition, and discharge status were not significantly different between responders and non-responders (Tables 15, 16). However, year of diagnosis, and sex and sexual status were significantly different (Table 16).

Table 16. Comparison of year of diagnosis, body condition, sex and sexual, and discharge status in 227 responders and 157 non-responders of the telephone questionnaire including 198 dogs diagnosed with pancreatitis and 186 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005. Data was extracted from the medical records.

Variable	No. dogs	No. responders	P value*
Year of diagnosis; n=384			0.014
2000	57	28	
2001	57	26	
2002	56	29	
2003	55	39	
2004	86	57	
2005	73	48	
Body condition; n=348			0.120
Underweight	68	35	
Normal weight	159	104	
Overweight	121	70	

Table 16. Continued

Variable	No. dogs	No. responders	P value*
Sex and sexual status; n=384			0.048
Spayed female	166	111	
Intact female	30	14	
Castrated male	127	69	
Intact male	61	33	
Discharge status; n=384			0.081
Alive	291	172	
Euthanized	80	51	
Died	13	4	

*P value based on Pearson chi-square test

Discussion

Dietary factors extracted from the medical records or recorded through the telephone questionnaire demonstrated a significant association with pancreatitis. An unusual ingestion showed the largest increase in odds of pancreatitis out of all dietary factors in the medical records search and the second largest from the telephone questionnaire. This suggests exposure of the pancreas to an unusual food may be one of the most important aspects of the association between diet and pancreatitis. Getting into the trash the week before disease diagnosis showed the highest odds of pancreatitis out of all measures of dietary factors. There was no exposure to trash in the control group

resulting in an undefined upper limit of the 95% CI, however it was still possible to estimate the OR using exact methods. This strong association might be due to the type of items dogs are likely to find in the trash. For example, trash could contain lower quality food, such as fat trimmings or expired food, than what an owner may feed the dog as treats. The strong association observed might also be due to the pancreas being exposed to substances it is normally not exposed to, if the dog does not normally get into the trash. Feeding table scraps the week before diagnosis, and feeding table scraps regularly throughout life were associated with the same increase in the odds of pancreatitis. There was extensive overlap between these two groups. Those owners that regularly gave their dogs table scraps continued to do so during the week before diagnosis. Dogs that did not eat table scraps the week before diagnosis that usually did regularly were those that could possibly have been anorexic. These groups would indicate repeated exposure to a particular type of food that might lead to pancreatitis. There were some owners who did not regularly feed table scraps but fed table scraps to anorectic dogs in an attempt to get them to eat during the week before bringing them to TAMU SAC. In this case, the pancreatitis could have been caused by another factor, or the anorexia could have been due to pancreatitis that had already developed. The odds of pancreatitis due to feeding table scraps based on information extracted from the medical records, and presence at a family party the week before diagnosis were not significantly associated with pancreatitis. The exposure to any dietary factor based on information from both the medical records and the telephone questionnaire were similar in their associations with pancreatitis. According to these results, dietary factors do increase the odds of

pancreatitis. These results agree with anecdotal data concerning the association between diet and pancreatitis. This association may be due to particular substances that may lead to pancreatitis, such as dietary fat, as has been suggested in experimental pancreatitis.[3,4]

The median age for the case group was 8 years, which was not significantly different from the control group, and was similar to findings reported elsewhere for spontaneous pancreatitis.[1,2,17] These data suggest that pancreatitis is more common in middle-aged dogs. Being overweight, or even obesity, which had an increased odds of pancreatitis in bivariable analysis, and a confounding effect in multivariable analysis in this study, has been shown to be more prevalent in older dogs.[32,33] The prevalence for obesity appears to increase up to about 10 years of age.[32]

The medians for body weight were significantly different between the case and control groups. The lower weight of the dogs diagnosed with pancreatitis could be due to a genetic predisposition of pancreatitis among smaller dog breeds. It could also be due to diet. As breed size increases, dry dog food ingestion appears to increase, and table scraps ingestion appears to decrease among pet dogs.[33] Thus, smaller dogs, which also have a lower body weight may be at increased risk for pancreatitis.

Neutered dogs and castrated males had increased odds for developing pancreatitis. Neutered dogs may have an increased risk of obesity or being overweight.[32,34] However, the multivariable model included the variable overweight, which should have controlled for confounding. Spayed females relative to all others did not appear to have an increased risk of pancreatitis in this study, which contradicts what has been reported in previous studies.[1,2]

Some dog breeds that have been reported to be at increased risk for pancreatitis in previous studies,[1,2] also had an increased odds of pancreatitis in this study. These breeds included Miniature Schnauzers, Yorkshire Terriers, and terriers as a group. The current study did not find an association between the non-sporting breeds, Labrador Retrievers or Miniature Poodles and pancreatitis, as has been reported elsewhere.[1,2] The breed associations might indicate a genetic predisposition for pancreatitis. This could also be due the type of diet fed, as table scraps feeding by owners appears to increase with decreasing body size of the pet dog.[33]

Undergoing surgery at any time prior to disease diagnosis increased the odds of pancreatitis. This could be due to exposure to anesthetic agents, trauma to the pancreas during surgery, or hypoperfusion of the pancreas during surgery. Intact dogs that underwent surgery prior to disease diagnosis had a drastic increase in the odds of pancreatitis, while neutered dogs that underwent another surgery prior to diagnosis did not have an increased odds of pancreatitis. The type of surgery that the dogs underwent also had a drastic effect on the association with pancreatitis among intact dogs with invasive surgery having higher odds of pancreatitis than non-invasive surgery relative to no surgery. Sexual status seems to affect the association between prior surgery and pancreatitis.

The lack of a significant association between pancreatitis and a temporal proximity to a holiday agrees with a previous study that also was unable to identify an association.[1] This may be due to the referral pattern of private veterinary hospitals. The date of the referral may not be related to the initial onset of disease. Both, the previous

and the current study were based on referral patients. A different study population might therefore allow for the detection of a temporal association of holidays with pancreatitis.

Diagnosis of pancreatitis at TAMU SAC increased significantly from 2000-2003 to 2004-2005. This coincides with the development and validation of the canine pancreatic lipase immunoreactivity (cPLI) assay.[30] This suggests that the disease might be more readily diagnosed, rather than that the true prevalence of the disease is increasing. The prevalence of renal failure did not change over the same time period. It is also possible that referral patterns from private veterinary hospitals changed over the course of this study.

A lack of validity in a study, known as bias, can develop from a systematic error in the data and can be due to three main reasons: selection bias, information bias, and confounding.[35] A selection bias occurs when the individuals chosen for study are not representative of the population of interest.[35] In a case-control study, the case definition determines the population that is being studied, and selection bias occurs when the control group does not represent the source population from which the cases were selected.[35]

The control group was selected from the same referral hospital as the case group in order to control for referral patterns to the hospital. A random sample of the general population would not comprise dogs that presented to the referral hospital that the case dogs presented to, and thus would not consider the referral patterns of that hospital. Renal failure was chosen as the control disease because it has a similar severity and frequency of admission to the TAMU SAC as pancreatitis. This is important because

individuals of the control group should have the same likelihood of presenting to TAMU SAC as individuals from the source population. Renal failure was chosen as the control disease because it is not known to be associated with the primary exposure of interest, dietary factors. If exposed dogs are more likely to be hospitalized for renal failure than non-exposed dogs, the control group would be biased and the measure of effect would be biased toward the null (OR=1). This is because a dog with renal failure would be more likely to present to TAMU SAC upon illness than the average dog from the source population.

There are a couple of limitations to a renal failure control group. Dogs with renal failure are often on high-fat diets and are anorectic and thus receive more table foods or high-fat foods than the general referral population. Both of these could falsely decrease the association between dietary factors and pancreatitis.

The association between response proportion and selection bias is complex,[36] and a high response proportion may be important for data validity.[37] A low response proportion could mean that non-responders were systematically different from the responders and could introduce bias into the study.[36,37] This bias will occur if the exposure of interest is associated with the study subject's willingness to participate.[36] It is also possible for a study with a low response proportion to have less responder bias than a study with a high response proportion.[36] In order to estimate the effect of responder bias on the odds ratio, information on the non-responders is necessary to compare to the responders.[38] The response proportion of this study was 59%, and the non-responder analysis did not suggest important differences.

Descriptive analyses comparing telephone questionnaire responders to non-responders were carried out to assess for responder bias. The significant differences between the two groups included median weight, year of diagnosis, and sex and sexual status. The weight was lower in the non-responders, but only slightly so (responders, 26.6 lbs; non-responders, 22.4 lbs). The difference of responders versus the non-responders in the year of diagnosis of pancreatitis or renal failure in their dogs may be due to the fact that it was more difficult to contact owners who had brought their dog to TAMU SAC earlier during the study period. Address and telephone number changes were more common for owners of patients seen during the earlier dates. Responders had twice as many spayed female dogs than did non-responders. The sex and sexual status difference between responders and non-responders was stratified by disease diagnosis (pancreatitis or renal failure), and the same patterns were seen between responders and non-responders for the ratio of pancreatitis to renal failure for each sex and sexual status group. Even though responders had twice as many spayed females as non-responders, the association between sex and sexual status and pancreatitis was the same.

Recall bias is a possibility in case-control studies, especially when there is a substantial time lag between diagnosis and questionnaire administration. Veterinarians who suspect pancreatitis will often question and educate clients more thoroughly on the effect of diet, compared to veterinarians who suspect renal failure. Clients who may have been more thoroughly questioned during the time of admission may be more likely to remember what their dog was eating around the time of diagnosis. This can introduce a recall bias among the telephone questionnaire participants. If the owners of the renal

failure dogs do not recall their dog's eating habits, and do not report exposure to dietary factors that occurred, and the owners of pancreatitis dogs do recall their dog's eating habits and report the exposure to dietary factors, the measure of association would be biased away from the null. The results of the telephone questionnaire were similar to the results of the medical records search, suggesting that recall bias did not have a large impact on these results. However, it is possible that any client who brings their dog to a referral hospital is equally likely to remember the aspects of their dog's diet around the incidence of the disease.

Conclusion

Dietary factors increase the odds for spontaneous pancreatitis in dogs. Increasing the awareness concerning important risk factors will contribute to better prevention, diagnosis, and management of pancreatitis in dogs. This in turn may decrease morbidity and mortality associated with this important condition. This increased understanding together with client education may increase owner motivation to avoid inappropriate dietary exposure to their dog.

CHAPTER III

DISCUSSION AND CONCLUSION

A retrospective case-control study was performed to accomplish the objectives of this study which were to determine if dietary factors predispose dogs to spontaneous pancreatitis and to identify non-dietary variables that are associated with pancreatitis in this study population.

In case-control studies, participants are chosen based on their disease status.[35] The case definition determines the source population, or study base, from which cases are selected,[35] and the control group should represent the exposure distribution of the source population from which the cases were selected.[35] The exposure distribution is compared between the case group and the control group to estimate the effect of the exposure on disease status.[35] The appropriate measure of effect is the odds ratio.[35] The risk ratio is inappropriate because of the artificially increased prevalence of disease in the study population.[35] Case-control studies are efficient and simple to perform and analyze. However, they are very difficult to design well because they are susceptible to many biases.

The study base represents the source population for cases during the time they were eligible to become cases, and should be represented equally by the cases and controls.[39] Controls are included in the base if they meet the criteria to become a case provided they are diagnosed with the disease of interest during the time describing the base. There is a primary base approach and a secondary base approach. A primary base is when the investigator defines the source population first, and then attempts to identify

all cases within that source population.[39] The primary base is defined primary to case identification. A challenge of the primary base approach is identifying all of the cases within the study base. A secondary base is when the investigator identifies the cases first, and the source population is defined secondary to the case definition.[39] Cases are identified from a registry, such as a referral hospital, and the source population describes all individuals that would have presented to that hospital had they gotten the disease of interest.[39] A challenge of the secondary base approach is accurately defining the source population. This study used the secondary base approach, the study base being the referral hospital to which all dogs admitted with a first time diagnosis of pancreatitis within a six-year period were included as a case. In order for the control group to be representative of the exposure distribution of the source population from which the cases were selected, it should be chosen from the same study base.[39]

Case-control studies are susceptible to selection bias, information bias, and confounding. Selection bias occurs whenever the group of individuals being studied is not representative of the population of interest. The biggest difficulty in designing a case-control study well is in the selection of the control group. Poor selection of the control group leads to selection bias. Another form of selection bias, known as responder bias occurs in surveys when not all individuals chosen in the case group and control group participate. The bias occurs when the responders are systematically different from the non-responders in respect to the exposure-disease relationship. Information bias can occur whenever information is not collected in precisely the same way between cases and controls. Interviewer bias occurs when the person collecting the data influences

study participants in an intentional or unintentional effort to obtain the data that they expect. Recall bias occurs when one group under study more accurately remembers the exposure than the comparison group. Detection bias occurs when more effort is put into collecting data on the exposure from one group over another. Confounding results when a risk factor for the outcome is also associated with the exposure without being on the direct causal pathway and confuses the association between the exposure and the outcome.

A considerable effort must be placed into the design of a case-control study. Recognition of potential sources of bias during the design phase is the only way to control for selection and information bias. Confounding can be controlled during data analysis by including potential confounding factors in the logistic regression model if valid data for these variables were appropriately collected. The odds ratio should be a good estimate of the risk ratio in a well-designed study. This is important for interpretation of the odds ratio in terms of disease incidence.

Dietary factors, including any food intake other than a commercially manufactured dog food or a homemade diet prescribed by a veterinarian, are commonly accepted as risk factors for pancreatitis. Dietary factors associated with spontaneous pancreatitis in dogs have not been previously evaluated. It has been noted that the onset of clinical signs of pancreatitis in some patients can follow ingestion of a fatty food.[23] A high-fat diet has been shown to induce[3] and increase the severity[4] of experimental canine pancreatitis. However, when risk factors for spontaneous canine pancreatitis have been evaluated, dietary factors have been excluded from the analysis.[1] This was because of

the method of data collection. In a retrospective investigation involving the collection of data from medical records for factors that may predispose dogs to the development of a disease, the investigator is limited to the information that has been recorded in the medical record for each patient. This limitation could introduce information bias into the study if the investigator evaluates diet as a risk factor for pancreatitis because owners with dogs that are showing clinical signs of pancreatitis may be more thoroughly questioned about the dog's food intake than owners with dogs that are not showing signs of pancreatitis.[1] When the case group is more thoroughly questioned about such risk factors of interest, detection bias can be introduced into the study.[40] This source of bias was minimized by use of a standardized questionnaire that clients completed while in the waiting room of the TAMU SAC. This questionnaire included questions on diet and a standardized protocol that senior veterinary students follow when recording the history of their patients while in the exam room. The potential bias still exists, but has been minimized.

Another difficulty in using medical records alone to assess dietary factors is the inability of the investigator to know how the owners were questioned concerning the food intake of their dog. A standardized set of questions were employed to prevent bias[40] and exclusion of potentially important information. By using a telephone survey to question owners concerning the food intake of their dog during the week prior to being diagnosed with disease at the TAMU SAC, both the case group and the control group were asked the same questions in a blinded manner, using a standardized approach. This allowed for the evaluation of dietary factors while minimizing potential sources of bias.

The possibility of recall bias is created by the study of a disease, for which an anecdotal association with a risk factor is suspected. Diet is commonly accepted as a risk factor for pancreatitis, but it is not believed to be a risk factor for renal failure. Veterinarians who suspect pancreatitis will often question and educate clients more thoroughly on the effect of diet on the potential diagnosis than veterinarians who suspect renal failure, or other diseases. Clients who are questioned more thoroughly about the diet of their dog or who are given the impression that the diet may negatively influence their dog might be more likely to remember what their dog had eaten around the time of diagnosis compared to clients who did not get the impression that their dog's health was related to the diet. This can introduce recall bias among the telephone questionnaire participants if individuals in the case group remember their dog's exposure to dietary factors better than those in the control group or if they are more likely to remember an exposure incorrectly. Recall bias in general is when the errors in recall are not equal between the groups. Because the crude ORs of the telephone questionnaire concerning dietary factors were similar to those of the medical records search concerning dietary factors, recall bias is less likely to have been an important problem. Recall bias is less of a concern for the data extracted from the medical records. Due to the difficulty of diagnosing pancreatitis, it is likely that many of the dogs who presented at TAMU SAC were referred for a diagnosis, and the owners may not have received an impression from the referring veterinarian concerning the effect of diet on their dog's health.

Those clients who bring their dogs to a referral hospital represent a group of individuals who seek extra care for their pets, and could be more likely to remember all

aspects of their dog's health around the incidence of disease. The telephone questionnaire participants were asked what disease their dog was diagnosed with at TAMU SAC. With one exception, the disease reported during the telephone questionnaire agreed with the disease reported in the medical record for both cases and controls. This is an indication that the owners of the case and control groups remembered the visit they were being questioned about with equal accuracy. This is more evidence that recall bias was less likely to have been an important problem in this study.

A second multivariable logistic regression model was built using "exposures to one or more dietary factors" extracted from the medical records as the primary exposure of interest. The same steps were followed as for the previous model, and a similar model was built (Table 17). The models are similar, with the main difference being the measure of effect for the primary variable of interest. According to the data extracted from the medical records, dietary factors do not significantly increase the odds of pancreatitis. It is impossible to determine which model is a more accurate representation of the time association.

The variable "exposure to one or more dietary factors" was compared between the medical records search and the telephone questionnaire by calculating kappa (Table 18). The kappa statistic is a measure of agreement between two or more categorical variables. A kappa of zero indicates there is no more agreement between the two variables beyond what would be expected by chance. A kappa of one indicates perfect

Table 17. Multivariable logistic regression model for the estimation of measures of association between variables and spontaneous pancreatitis in 94 dogs diagnosed with pancreatitis and 92 control dogs diagnosed with renal failure from the TAMU SAC during the period of 2000 to 2005.

Variable	**Parameter estimate ($\hat{\beta}$)**	**P value (Wald)**	**Odds ratio (95% CI)**
Any inappropriate dietary factor	0.49	0.136	1.6 (0.9, 3.1)
Overweight	0.49	0.155	1.6 (0.8, 3.2)
Year of diagnosis (dichotomized)	1.2	0.0003	3.3 (1.7, 6.2)
Non-neuter surgery	2.89	0.002	17.9 (2.8, 112.8)
Sexual status	1.28	0.011	3.6 (1.3, 9.5)
Neuter by non-neuter surgery interaction	-2.67	0.009	0.07 (0.01, 0.51)

LogOdds(pancreatitis)=β_1(diet) + β_2(overweight) + β_3(year) + β_4(surgery) + β_5(neuter) + β_6(neuter*surgery) + β_0

agreement, and a negative kappa indicates that the agreement is weaker than what would be expected by chance. The kappa statistic shows poor agreement between the two data collection methods for this variable (Table 18). This could be due to recall bias or differential misclassification. The recall bias could be due to the time difference

Table 18. Agreement between the medical records and telephone questionnaire as methods of data collection for the variable "exposure to one or more dietary factors".

	n	kappa	P value
Respondents	204	0.213	0.001
Cases	108	0.242	0.011
Controls	96	0.140	0.125
2000	27	0.293	0.093
2001	19	-0.080	0.729
2002	25	-0.115	0.561
2003	34	0.391	0.009
2004	54	0.267	0.044
2005	45	0.262	0.065

between when the dogs were diagnosed at the TAMU SAC and the owners participated in the questionnaire. It could also be due a difference in owner education received at the TAMU SAC between the case group and the control group as mentioned previously. Differential misclassification is due to a systematic error in the data that can bias the measure of effect either toward or away from the null. It is not possible to know which direction the bias will take, and can not be adjusted for in the analysis.

Because of the nature of owner who brings their dog to a referral hospital, the source population of the case group is limited to dogs that would present at a referral hospital for disease diagnosis. The owner population that responded to the telephone

questionnaire had a median age of 53 years, 65.2% had a college degree, over half earned $70,000 or more annually, and 93.4% where white. According to a 2005 annual demographic questionnaire by the U.S. Census Bureau,[41] the 2005 United States population had a median age of 36.4 years, 9.3% had a college degree, the median annual income was $46,242, and 74.7% were white. Thus, the owners of the dogs in this study are not representative of the general population. This does not preclude generalizability of the findings from this study. The case group and the control group were selected with the main objective of minimizing sources of bias. This increases the strength of the study, and is more important than the study population being a representative subset of the general population. The likelihood of a dog presenting to TAMU SAC may be unrelated to the variables collected about owners in this questionnaire. There can be additional factors involved, such as the human-animal bond that were not addressed in this study.

Identification of the appropriate control group was a difficult task. The control group should represent the exposure distribution of the source population from which the cases were selected to minimize bias.[40] Dogs diagnosed with renal failure were used as a control group in an effort to reduce selection and information bias. Renal failure was thought to be similar to pancreatitis in disease severity and rate of admission to the small animal clinic. This observation was made by an internal medicine clinician in the TAMU SAC (Mike Willard, personal communication, April 12, 2006), and was also observed by comparing the TAMU SAC medical records database for pancreatitis and renal failure. When selecting hospital-based cases and controls with comparable diseases, the

admission rate of the control group should be similar to the case group to obtain an unbiased odds ratio.[42]

Exposure to the risk factor of interest should not affect admission rate to the hospital for the selected control group to prevent underestimation of the true odds ratio.[42,35] For this study, only food items were included in the definition of dietary factors. If dietary factors predispose dogs for renal failure, then the association between dietary factors and pancreatitis will be biased towards the null.[40]

Control dogs with a concurrent diagnosis of any disease that could be caused by dietary factors or be the primary reason for the visit were excluded from the control group. This was done to ensure that controls were selected independently of the exposure in the source population and the control group was presenting to TAMU SAC for renal failure rather than another disease. The control group disease should not be associated with the case group disease. An association between the two diseases would create selection bias because the exposure distribution of the control group would be higher than that in the source population.[42]

Control dogs with a prior history of pancreatitis but without a concurrent diagnosis of another disease were included as valid controls. Exclusion criteria based on pancreatitis history does not improve the representativeness of the control group relative to the source population.[35] If there is a true association between dietary factors and pancreatitis, exclusion would result in an under-representation of the exposure distribution of the source population in the control group, and would result in an upward bias in the odds ratio.[35]

A drawback of using renal failure as the control group in this study was the common clinical sign of anorexia. An owner of an anorectic dog may feed anything in an attempt to entice their pet to eat. This, however, can be true of any disease that results in anorexia. Veterinarians will instruct owners to feed the dog whatever it will eat in an attempt to maintain nutrition in an anorectic dog. Anorexia is also a common clinical sign of pancreatitis. In this study, 5% of the telephone respondents from the control group who did not regularly feed their dog table scraps reported that they fed their dog anything in an attempt to get it to eat. This was in response to when they were asked what they fed their dog during the week before diagnosis at TAMU SAC. This might have caused an underestimation of the odds ratio for the variables "table scraps the week before diagnosis" or "exposure to one or more of the dietary factors". The odds ratios calculated in this study indicate that all dietary factors studied are associated with an increased odds of pancreatitis. Bias is more of a concern in this study when it causes an overestimation of the odds ratio, potentially indicating an association when in reality one is not present.

The order of mailings was randomly assigned among the cases and controls. This was to blind the investigator to case/control status of the dogs while conducting the telephone questionnaire. The telephone questionnaire was referred to as a canine health questionnaire to the respondents, and they were asked general health questions about their dogs in addition to questions concerning the diet to blind the respondents to the disease being studied.

The questionnaire concluded with owner demographic questions. This was the most difficult part of the questionnaire. Some respondents felt uncomfortable supplying demographic information and declined to answer. Most respondents complied, however some of those respondents felt that the questionnaire investigator was less trustworthy because the owner demographic information was included. They questioned whether the questionnaire was being conducted by someone affiliated with Texas A&M University (TAMU) because they did not understand why TAMU would want to know their demographic information.

Of the non-respondents, thirteen people were reached on the telephone and declined to participate. The remainder was not reachable on the telephone. According to the investigator's memory, two reasons were given for declining to participate. It was either too painful for the owner to talk about their dog, or they were unhappy with their dog's treatment at TAMU SAC. There were a few respondents who were unhappy with their dog's treatment at TAMU SAC, but participated to improve knowledge of dog diseases. The majority of respondents was very happy with their dog's treatment at TAMU SAC, remembered the name of the clinician who worked with them, and wanted updates on the TAMU SAC. Three respondents asked for a copy of the published results of the questionnaire.

This study could be improved by adding another control group. It is not known with certainty that dietary factors are not associated with the incidence of renal failure. Using more than one comparable disease for the control group could dilute potential bias that would be caused by inadvertently using a control disease that is associated with the

exposure of interest. This could also increase bias if the investigator inadvertently chooses multiple control diseases that are all associated with the exposure of interest. This study could also be improved by using a control disease that does not cause anorexia. Dogs that are loosing weight due to anorexia may be fed anything by their owner in an attempt to entice the dog to eat. It is possible that by feeding an anorectic dog table scraps, the owner is inadvertently inducing pancreatitis in the dog. Conversely, pancreatitis is known to lead to multiple organ failure which can include renal failure. With a concurrent diagnosis of renal failure and pancreatitis, it is difficult to know which disease came first, or which disease is the primary reason for the veterinary visit. When that occurred in this study, those dogs were excluded from the analysis. Dogs diagnosed with chronic renal failure were likely prescribed a specific diet to help manage the renal failure. The owners are usually instructed to strictly monitor their dog's food intake, and the diet prescribed is high in fat. A dog with a strictly monitored diet is less likely to be exposed to the dietary factors evaluated in this study, thus increasing the measure of effect between dietary factors and pancreatitis. However, a dog fed a prescription high fat diet may have an increased likelihood of concurrent pancreatitis without the exposure to the dietary factors evaluated in this study, leading to exclusion of the dog as a study participant and possibly decreasing the association between dietary factors and pancreatitis.

Telephone questionnaires are complex. It is difficult to compose questions that the investigator can ask the respondents that convey the concepts being asked in such a manner that both explains what information is wanted and triggers the response desired

with minimal confusion or influence by the respondent. It is important to ask questions that do not frustrate the respondent or cause them grief. It is very difficult to ask the same question repeatedly without starting to sound mechanical. It is also important not to have preconceived notions about what answer should be given.

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APPENDIX A

Table A-1. Descriptive statistics of the continuous variables for the case group. Data were collected from the medical record† and a telephone questionnaire▲ for the date of visit.

Variable	Pancreatitis (cases)				
	Mean	**Median**	**Interquartile range**	**Standard deviation**	**Kolmogorov-Smirnov P value**
Dog age (years)†	7.88	8.00	6.00	3.806	0.000
Weight (lbs)†	30.52	20.00	34.00	24.649	0.000
Hospital stay (days)†	4.0	3.0	5.0	4.30	0.000
IV fluids (days)†	2.5	2.0	4.0	2.58	0.000
cPLI (µg/L)†	362.06	333.00	389.50	276.074	0.036
Owner's age (years) ▲	52.06	54	19	12.811	0.034

Table A-2. Descriptive statistics of the continuous variables for the control group. Data were collected from the medical record† and a telephone questionnaire▲ for the date of visit.

Variable	Renal Failure (controls)				
	Mean	**Median**	**Interquartile range**	**Standard deviation**	**Kolmogorov-Smirnov P value**
Dog's age (years)†	7.23	7.00	7.00	4.270	0.000
Weight (lbs)†	39.38	32.65	45.00	29.234	0.000
Hospital stay (days)†	2.9	1.0	4.0	3.70	0.000
IV fluids (days)†	1.9	0.5	3.0	2.86	0.000
cPLI (µg/L)†	203.37	148.30	194.20	108.179	0.128*
Owner's age (years) ▲	50.87	51	13	11.043	0.09

*The Shapiro-Wilk P value is given because the number of data points was less than 50. This P value is based on three data points, and this variable will not be considered normally distributed.

Table A-3. Mann-Whitney U test for equality of medians of the non-normally distributed, continuous variables between the case and the control group. Data were collected from the medical record† and a telephone questionnaire▲ for the date of visit.

Variable	Mann-Whitney U test	
	Z	P value
Dog's age (years) †	-1.623	0.105
Weight (lbs) †	-3.059	0.002
Hospital stay (days) †	-2.996	0.003
IV fluids (days) †	-2.916	0.004
cPLI (µg/L) †	-1.022	0.328
Owner's age (years) ▲	-0.837	0.402

Table A-4. Comparison of the variable "sex of the dog" between the case group and the control group. Data were collected from the medical record for the date of visit.

Sex	Disease		Total
	Pancreatitis	Renal Failure	
Male	99	89	188
Female	99	97	196
Total	198	186	384

Crude OR: 1.090; 95% CI: (0.730, 1.627); Pearson chi-square P value: 0.674

Adjusted OR: 1.112; 95% CI: (0.744,1.663); Mantel-Haenszel chi-square P value: 0.605

Table A-5. Comparison of the variable "sexual status" between the case group and the control group. Data were collected from the medical record for the date of visit.

Neutered	Disease		Total
	Pancreatitis	Renal Failure	
Yes	168	125	293
No	30	61	91
Total	198	186	384

Crude OR: 2.733; 95% CI: (1.667, 4.481); Pearson chi-square P value: 0.00005

Adjusted OR: 2.682; 95% CI: (1.631, 4.408); Mantel-Haenszel chi-square P value: 0.0001

Table A-6. Comparison of the variable "sexual status" in male dogs, between the case group and the control group. Data were collected from the medical record.

Male dogs	Disease		Total
	Pancreatitis	Renal Failure	
Castrated	80	47	127
Intact	19	42	61
Total	99	89	188

Crude OR: 3.763; 95% CI: (1.963, 7.212); Pearson chi-square P value: 0.00004

Adjusted OR: 3.690; 95% CI: (1.922, 7.084); Mantel-Haenszel chi-square P value: 0.0009

Table A-7. Comparison of the category "castrated male" and all other sex and sexual status categories, between the case group and the control group. Data were collected from the medical record.

Castrated male	Disease		Total
	Pancreatitis	Renal Failure	
Yes	80	47	127
No	118	139	257
Total	198	186	384

Crude OR: 2.005; 95% CI: (1.297, 3.100); Pearson chi-square P value: 0.002

Adjusted OR: 2.027; 95% CI: (1.308, 3.141); Mantel-Haenszel chi-square P value: 0.002

Table A-8. Comparison of the variable "Miniature Schnauzer" breed between the case group and the control group. Data were collected from the medical record.

Miniature Schnauzer	Disease		Total
	Pancreatitis	Renal Failure	
Yes	31	8	39
No	167	178	345
Total	198	186	384

Crude OR: 4.130; 95% CI: (1.846, 9.242); Pearson chi-square P value: 0.0002

Adjusted OR: 3.952; 95% CI: (1.760, 8.873); Mantel-Haenszel chi-square P value: 0.001

Table A-9. Comparison of the variable "Yorkshire terrier" breed between the case group and the control group. Data were collected from the medical record.

Yorkshire Terrier	Disease		Total
	Pancreatitis	Renal Failure	
Yes	13	3	16
No	185	183	368
Total	198	186	384

Crude OR: 4.286; 95% CI: (1.201, 15.293); Pearson chi-square P value: 0.015

Adjusted OR: 4.543; 95% CI: (1.244, 16.588); Mantel-Haenszel chi-square P value: 0.022

Table A-10. Comparison of the variable "Labrador Retriever" breed between the case group and the control group. Data were collected from the medical record.

Labrador Retriever	Disease		Total
	Pancreatitis	Renal Failure	
Yes	8	15	23
No	190	171	361
Total	198	186	384

Crude OR: 0.480; 95% CI: (0.199, 1.160); Pearson chi-square P value: 0.097

Adjusted OR: 0.490; 95% CI: (0.202, 1.191); Mantel-Haenszel chi-square P value: 0.115

Table A-11. Comparison of the variable "Miniature poodle" between the case group and the control group. Data were collected from the medical record.

Miniature Poodle	Disease		Total
	Pancreatitis	Renal Failure	
Yes	3	3	6
No	195	183	378
Total	198	186	384

Crude OR: 0.938; 95% CI: (0.187, 4.709); Pearson chi-square P value: 0.938

Adjusted OR: 1.046; 95% CI: (0.201, 5.450); Mantel-Haenszel chi-square P value: 0.957

Table A-12. Comparison of the variable "all Terrier breeds" between the case group and the control group. Data were collected from the medical record.

Terriers	Disease		Total
	Pancreatitis	Renal Failure	
Yes	44	19	63
No	154	167	321
Total	198	186	384

Crude OR: 2.511; 95% CI: (1.405, 4.489); Pearson chi-square P value: 0.001

Adjusted OR: 2.437; 95% CI: (1.359, 4.369); Mantel-Haenszel chi-square P value: 0.003

Table A-13. Comparison of the variable "grossly lipemic serum sample" between the case group and the control group. Data were collected from the medical record for the date of visit.

Lipemic	Disease		Total
	Pancreatitis	Renal Failure	
Yes	36	10	46
No	162	176	338
Total	198	186	384

Crude OR: 3.911; 95% CI: (1.880, 8.135); Pearson chi-square P value: 0.0001

Adjusted OR: 3.857; 95% CI: (1.833,8.117); Mantel-Haenszel chi-square P value: 0.0004

Table A-14. Comparison of the variable "concurrent hypothyroidism" between the case group and the control group. Data were collected from the medical record for the date of visit.

Hypothyroidism	Disease		
	Pancreatitis	Renal Failure	Total
Yes	18	17	35
No	180	169	349
Total	198	186	384

Crude OR: 0.994; 95% CI: (0.496, 1.993); Pearson chi-square P value: 0.987

Adjusted OR: 0.992; 95% CI: (0.492, 2.003); Mantel-Haenszel chi-square P value: 0.983

Table A-15. Comparison of the variable "concurrent hyperadrenocorticism" between the case group and the control group. Data were collected from the medical record for the date of visit.

Hyperadrenocorticism	Disease		
	Pancreatitis	Renal Failure	Total
Yes	8	5	13
No	190	181	371
Total	198	186	384

Crude OR: 1.524; 95% CI: (0.490, 4.746); Pearson chi-square P value: 0.464

Adjusted OR: 1.619; 95% CI: (0.517, 5.071); Mantel-Haenszel chi-square P value: 0.408

Table A-16. Comparison of the variable "concurrent Diabetes mellitus" between the case group and the control group. Data were collected from the medical record for the date of visit.

Diabetes mellitus	Disease		Total
	Pancreatitis	Renal Failure	
Yes	11	3	14
No	187	183	370
Total	198	186	384

Crude OR: 3.588; 95% CI: (0.985, 13.071); Pearson chi-square P value: 0.039

Adjusted OR: 3.938; 95% CI: (1.047, 14.812); Mantel-Haenszel chi-square P value: 0.043

Table A-17. Comparison of the variable "prior illness during lifetime of the dog" between the case group and the control group. Data were collected through the telephone questionnaire.

Prior illness	Disease		Total
	Pancreatitis	Renal Failure	
Yes	54	44	98
No	58	67	125
Total	112	111	223

Crude OR: 1.418; 95% CI: (0.834, 2.411); Pearson chi-square P value: 0.197

Adjusted OR: 1.376; 95% CI: (0.806, 2.350); Mantel-Haenszel chi-square P value: 0.242

Table A-18. Comparison of the variable "taking prescription medication" between the case group and the control group. Data were collected through the telephone questionnaire.

Prescription medications	Disease		Total
	Pancreatitis	Renal Failure	
Yes	35	29	64
No	77	80	157
Total	112	109	221

Crude OR: 1.254; 95% CI: (0.700, 2.247); Pearson chi-square P value: 0.447

Adjusted OR: 1.221; 95% CI: (0.684, 2.180); Mantel-Haenszel chi-square P value: 0.500

Table A-19. Comparison of the variable "current on vaccines" between the case group and the control group. Data were collected through the telephone questionnaire.

Vaccines	Disease		Total
	Pancreatitis	Renal Failure	
Current	110	104	214
Not current	2	7	9
Total	112	111	223

Crude OR: 3.702; 95% CI: (0.752, 18.229); Pearson chi-square P value: 0.086

Adjusted OR: 3.603; 95% CI: (0.737, 17.624); Mantel-Haenszel chi-square P value: 0.114

Table A-20. Comparison of the variable "on monthly heartworm prevention" between the case group and the control group. Data were collected through the telephone questionnaire.

Heartworm prevention	Disease		Total
	Pancreatitis	Renal Failure	
Yes	106	104	210
No	6	6	12
Total	112	110	222

Crude OR: 1.019; 95% CI: (0.318, 3.263); Pearson chi-square P value: 0.974

Adjusted OR: 1.011; 95% CI: (0.317, 3.228); Mantel-Haenszel chi-square P value: 0.985

Table A-21. Comparison of the variable "prior trauma during lifetime of the dog" between the case group and the control group. Data were collected through the telephone questionnaire.

Prior trauma	Disease		Total
	Pancreatitis	Renal Failure	
Yes	17	22	39
No	95	89	184
Total	112	111	223

Crude OR:0.724; 95% CI: (0.361, 1.452); Pearson chi-square P value: 0.362

Adjusted OR: 0.716; 95% CI: (0.356, 1.441); Mantel-Haenszel chi-square P value: 0.349

Table A-22. Comparison of the variable "prior surgery during lifetime of the dog" between the case group and the control group. Data were collected through the telephone questionnaire.

Prior surgery	Disease		Total
	Pancreatitis	Renal Failure	
Yes	106	79	185
No	6	32	38
Total	112	111	223

Crude OR: 7.156; 95% CI: (2.854, 17.945); Pearson chi-square P value: 0.000007

Adjusted OR: 7.090; 95% CI: (2.826, 17.786); Mantel-Haenszel chi-square P value: 0.00003

Table A-23. Comparison of the variable "prior surgery other than a neuter during lifetime of the dog" between the case group and the control group. Data were collected through the telephone questionnaire.

Non-neuter surgery	Disease		Total
	Pancreatitis	Renal Failure	
Yes	41	26	67
No	71	85	156
Total	112	111	223

Crude OR: 1.888; 95% CI: (1.053, 3.384); Pearson chi-square P value: 0.032

Adjusted OR: 1.824; 95% CI: (1.013, 3.285); Mantel-Haenszel chi-square P value: 0.045

Table A-24. Comparison of the variable "prior surgery other than a neuter during lifetime in intact dogs" between the case group and the control group. Data were collected through the telephone questionnaire.

Non-neuter surgery in intact dogs	Disease		Total
	Pancreatitis	Renal Failure	
Yes	8	2	10
No	7	28	35
Total	15	30	45

Crude OR: 16.000; 95% CI: (2.761, 92.716); Pearson chi-square P value: 0.0004

Adjusted OR: 20.385; 95% CI: (2.980, 139.420); Mantel-Haenszel chi-square P value: 0.002

Table A-25. Comparison of the variable "prior surgery other than a neuter during lifetime in a neutered dog" between the case group and the control group. Data were collected through the telephone questionnaire.

Non-neuter surgery in neutered dogs	Disease		Total
	Pancreatitis	Renal Failure	
Yes	33	24	57
No	64	57	121
Total	97	81	178

Crude OR: 1.225; 95% CI: (0.649, 2.312); Pearson chi-square P value: 0.532

Adjusted OR: 1.187; 95% CI: (0.626, 2.252); Mantel-Haenszel chi-square P value: 0.600

Table A-26. Comparison of the variable "year of diagnosis dichotomized based on a change in diagnostic criteria for pancreatitis" between the case group and the control group. Data were collected from the medical record for the date of visit.

Year of diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
2004-2005	96	63	159
2000-2003	102	123	225
Total	198	186	384

Crude OR: 1.838; 95% CI: (1.217, 2.775); Pearson chi-square P value: 0.004

Adjusted OR: 1.834; 95% CI: (1.213, 2.774); Mantel-Haenszel chi-square P value: 0.004

Table A-27. Comparison of the variable "one week proximity to a holiday" between the case group and the control group. Data were collected from the medical record for the date of visit.

One week proximity to a holiday	Disease		Total
	Pancreatitis	Renal Failure	
Yes	30	38	68
No	168	148	316
Total	198	186	384

Crude OR: 0.695; 95% CI: (0.411, 1.178); Pearson chi-square P value: 0.176

Adjusted OR: 0.703; 95% CI: (0.413, 1.196); Mantel-Haenszel chi-square P value: 0.193

Table A-28. Comparison of the variable “overweight” between the case group and the control group. Data were collected from the medical record for the date of visit.

Overweight	Disease		Total
	Pancreatitis	Renal Failure	
Yes	73	48	121
No	100	127	227
Total	173	175	348

Crude OR: 1.931; 95% CI: (1.233, 3.025); Pearson chi-square P value: 0.004

Adjusted OR: 1.936; 95% CI: (1.233, 3.041); Mantel-Haenszel chi-square P value: 0.004

Table A-29. Comparison of the variable “unusual food intake” between the case group and the control group. Data were collected from the medical record for the date of visit.

Unusual food intake	Disease		Total
	Pancreatitis	Renal Failure	
Yes	26	6	32
No	159	157	316
Total	185	163	348

Crude OR: 4.279; 95% CI: (1.714, 10.680); Pearson chi-square P value: 0.001

Adjusted OR: 4.027; 95% CI: (1.623, 9.994); Mantel-Haenszel chi-square P value: 0.003

Table A-30. Comparison of the variable “table food ingestion” between the case group and the control group. Data were collected from the medical record for the date of visit.

Table food ingestion	Disease		Total
	Pancreatitis	Renal Failure	
Yes	108	80	188
No	77	83	160
Total	185	163	348

Crude OR: 1.455; 95% CI: (0.952, 2.224); Pearson chi-square P value: 0.082

Adjusted OR: 1.482; 95% CI: (0.968, 2.270); Mantel-Haenszel chi-square P value: 0.070

Table A-31. Comparison of the variable “inappropriate food intake” including table food ingestion and unusual food intake between the case group and the control group. Data were collected from the medical record for the date of visit.

Inappropriate food intake	Disease		Total
	Pancreatitis	Renal Failure	
Yes	123	80	203
No	62	83	145
Total	185	163	348

Crude OR: 2.058; 95% CI: (1.335, 3.174); Pearson chi-square P value: 0.001

Adjusted OR: 2.071; 95% CI: (1.341, 3.200); Mantel-Haenszel chi-square P value: 0.001

Table A-32. Comparison of the variable "unusual food intake during the week prior to diagnosis at TAMU" between the case group and the control group. Data were collected through the telephone questionnaire.

Unusual food intake during the week prior to diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
Yes	25	5	30
No	89	108	197
Total	114	113	227

Crude OR: 6.067; 95% CI: (2.231, 16.499); Pearson chi-square P value: 0.0001

Adjusted OR: 6.071; 95% CI: (2.186, 16.860); Mantel-Haenszel chi-square P value: 0.001

Table A-33. Comparison of the variable "table scraps ingestion during the week prior to diagnosis at TAMU" between the case group and the control group. Data were collected through the telephone questionnaire.

Table scraps intake during the week prior to diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
Yes	46	27	73
No	68	86	154
Total	114	113	227

Crude OR: 2.155; 95% CI: (1.216, 3.817); Pearson chi-square P value: 0.008

Adjusted OR: 2.245; 95% CI: (1.258, 4.006); Mantel-Haenszel chi-square P value: 0.006

Table A-34. Comparison of the variable "table scraps ingestion regularly throughout life" between the case group and the control group. Data were collected through the telephone questionnaire.

Table scraps throughout life	Disease		Total
	Pancreatitis	Renal Failure	
Yes	44	25	69
No	70	88	158
Total	114	113	227

Crude OR: 2.213; 95% CI: (1.236, 3.962); Pearson chi-square P value: 0.007

Adjusted OR: 2.276; 95% CI: (1.262, 4.106); Mantel-Haenszel chi-square P value: 0.006

Table A-35. Comparison of the variable "getting into the trash during the week prior to diagnosis at TAMU" between the case group and the control group. Data were collected through the telephone questionnaire.

Getting into trash the week prior to diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
Yes	9	0	9
No	105	113	218
Total	114	113	227

Crude OR: 10.75; Value calculated by adding 1 to each cell. P value: 0.003

LogXact: Crude MUE OR: 13.24; Exact 95% CI: (2.054, infinity); P value: 0.0034

LogXact: Adjusted MUE OR: 12.91; Exact 95% CI: (2.001, infinity); P value: 0.0039

Table A-36. Comparison of the variable "present at a family party with food and guests during the week prior to diagnosis at TAMU" between the case group and the control group. Data were collected through the telephone questionnaire.

Present at a party the week prior to diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
Yes	7	2	9
No	107	111	218
Total	114	113	227

Crude OR: 3.631; 95% CI: (0.738, 17.872);Pearson chi-square P value: 0.092

Adjusted OR: 3.367; 95% CI: (0.672, 16.882); MH chi-square P value: 0.140

Table A-37. Comparison of the variable "inappropriate food intake including all dietary factors collected through the telephone questionnaire" between the case group and the control group. Data were collected through the telephone questionnaire.

All inappropriate food intake during the week prior to diagnosis	Disease		Total
	Pancreatitis	Renal Failure	
Yes	63	34	97
No	51	79	130
Total	114	113	227

Crude OR: 2.870; 95% CI: (1.663, 4.954); Pearson chi-square P value: 0.0001

Adjusted OR: 2.865; 95% CI: (1.661, 4.944); MH chi-square P value: 0.0001

Table A-38. Comparison of the variable "referred to TAMU by another veterinarian" between the case group and the control group. Data were collected from the medical record for the date of visit.

Referral	Disease		
	Pancreatitis	Renal Failure	Total
Yes	165	167	332
No	33	19	52
Total	198	186	384

Crude OR: 0.569; 95% CI: (0.311, 1.041); Pearson chi-square P value: 0.065

Adjusted OR: 0.6; 95% CI: (0.326, 1.106); Mantel-Haenszel chi-square P value: 0.101

Table A-39. Comparison of the variable "other pets in the household" between the case group and the control group. Data were collected through the telephone questionnaire.

Other pets in the household	Disease		
	Pancreatitis	Renal Failure	Total
Yes	81	77	158
No	31	34	65
Total	112	111	223

Crude OR: 1.154; 95% CI: (0.647, 2.057); Pearson chi-square P value: 0.628

Adjusted OR: 1.224; 95% CI: (0.678, 2.208); Mantel-Haenszel chi-square P value: 0.503

Table A-40. Comparison of the variable "owner's sex" between the case group and the control group. Data were collected through the telephone questionnaire.

Owner's sex	Disease		Total
	Pancreatitis	Renal Failure	
Male	30	22	52
Female	80	86	166
Total	110	108	218

Crude OR: 1.466; 95% CI: (0.782, 2.749); Pearson chi-square P value: 0.232

Adjusted OR: 1.496; 95% CI: (0.798, 2.807); Mantel-Haenszel chi-square P value: 0.209

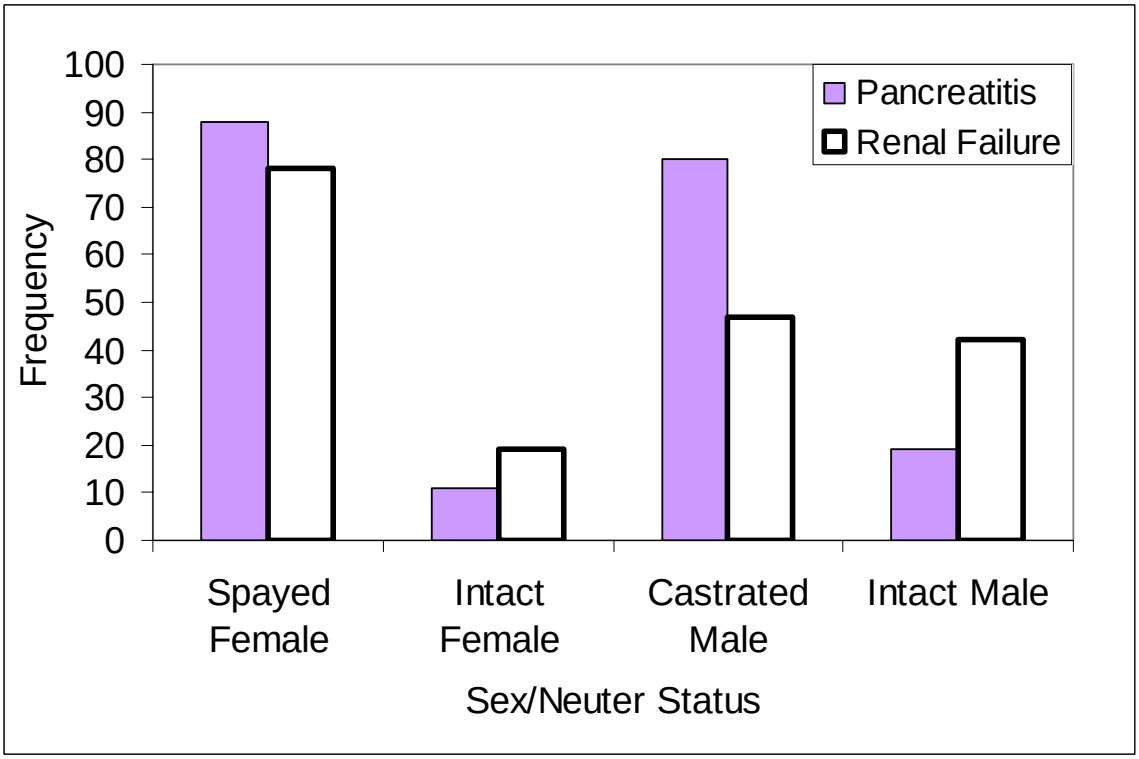

Figure A-1. Distribution of sex and sexual status for pancreatitis (cases) or renal failure (controls) patients.

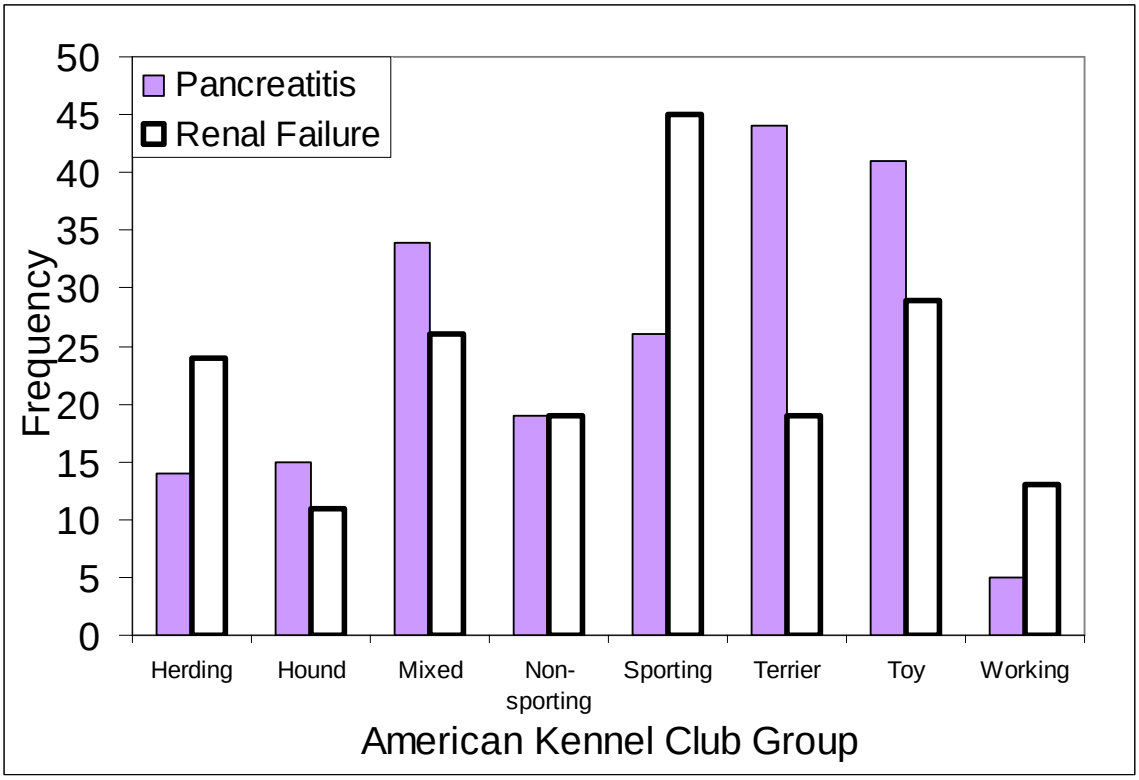

Figure A-2. Distribution of American Kennel Club dog breed groups for pancreatitis (cases) or renal failure (controls) patients.

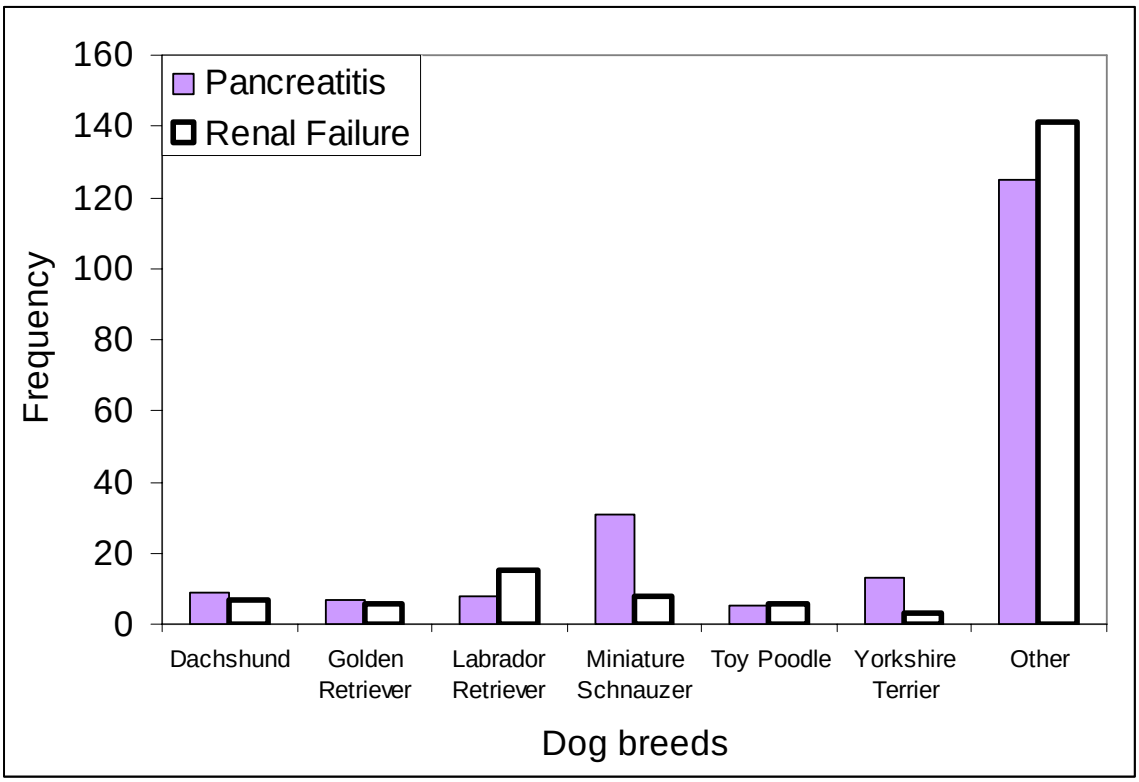

Figure A-3. Distribution of breeds with five or more dogs diagnosed with pancreatitis for pancreatitis (cases) or renal failure (controls) patients.

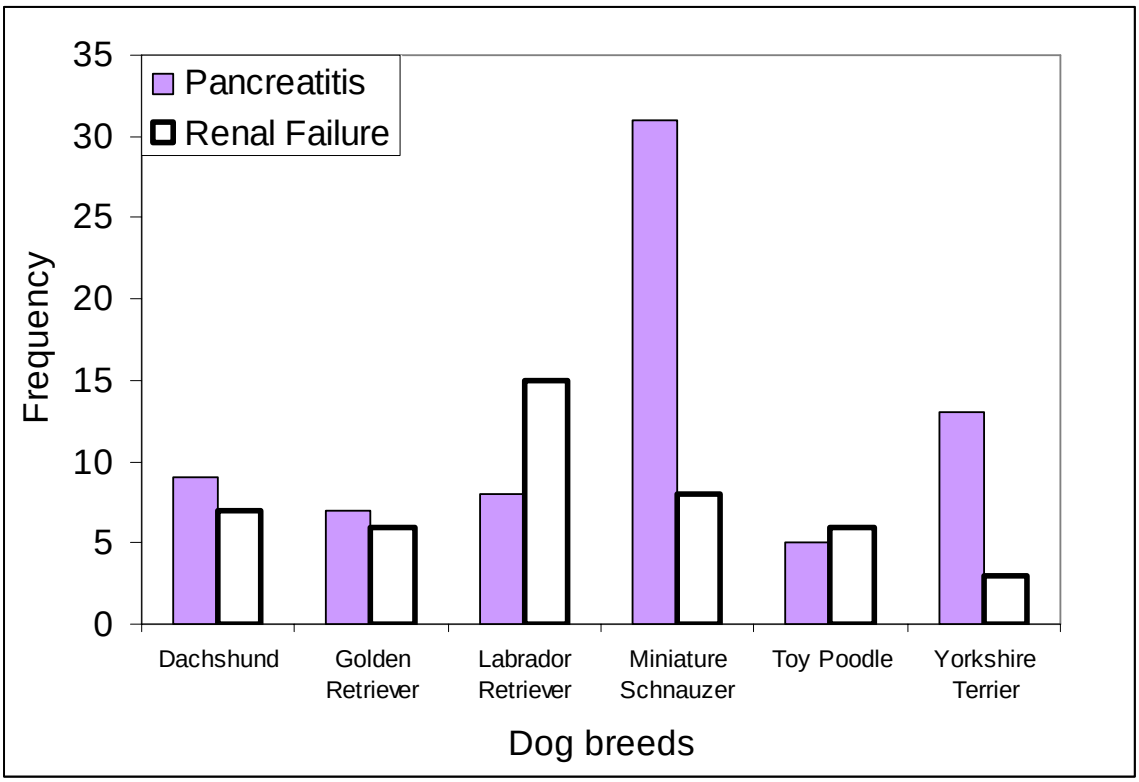

Figure A-4. Distribution of breeds with five or more dogs diagnosed with pancreatitis for pancreatitis (cases) or renal failure (controls) patients.

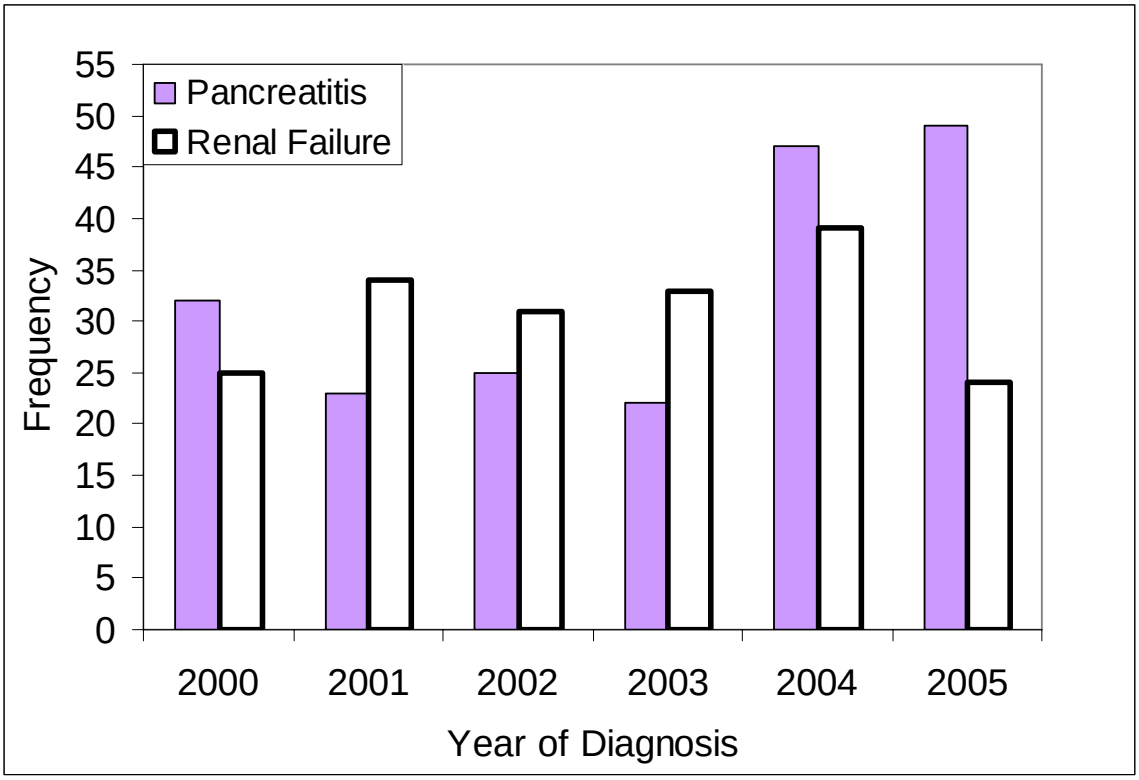

Figure A-5. Distribution of year of diagnosis for pancreatitis (cases) or renal failure (controls) patients.

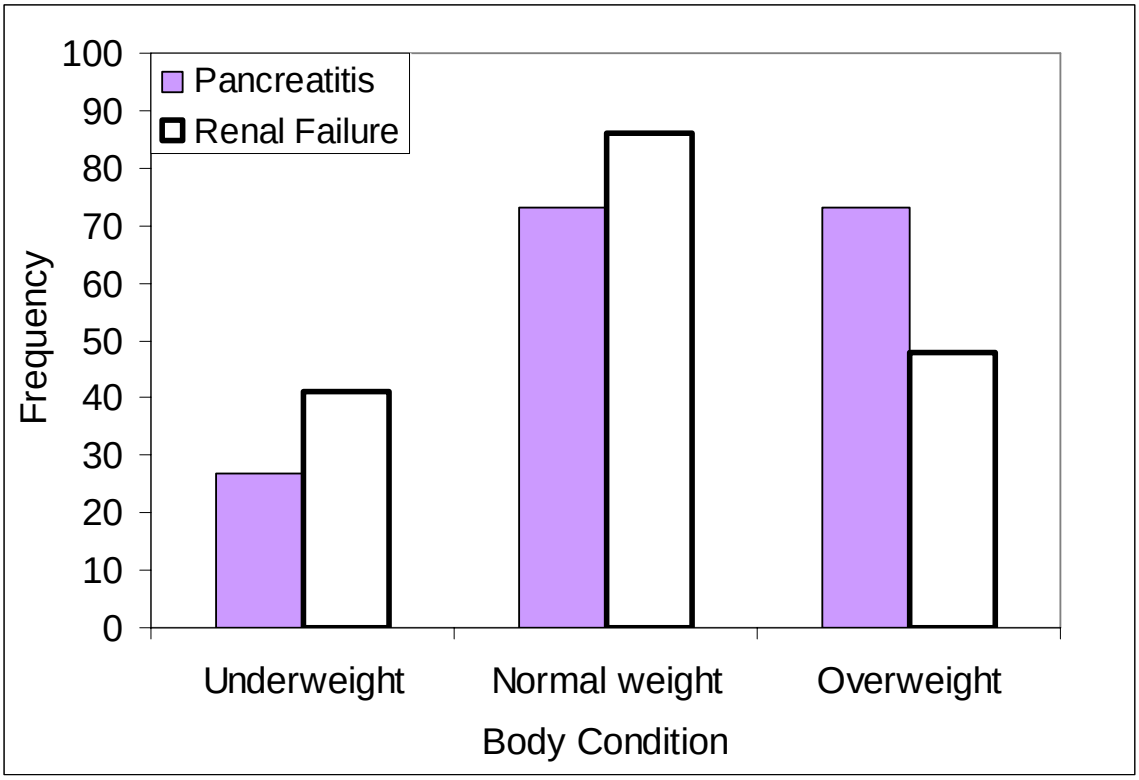

Figure A-6. Distribution of body condition at the time the dog presented at the hospital for pancreatitis (cases) or renal failure (controls).

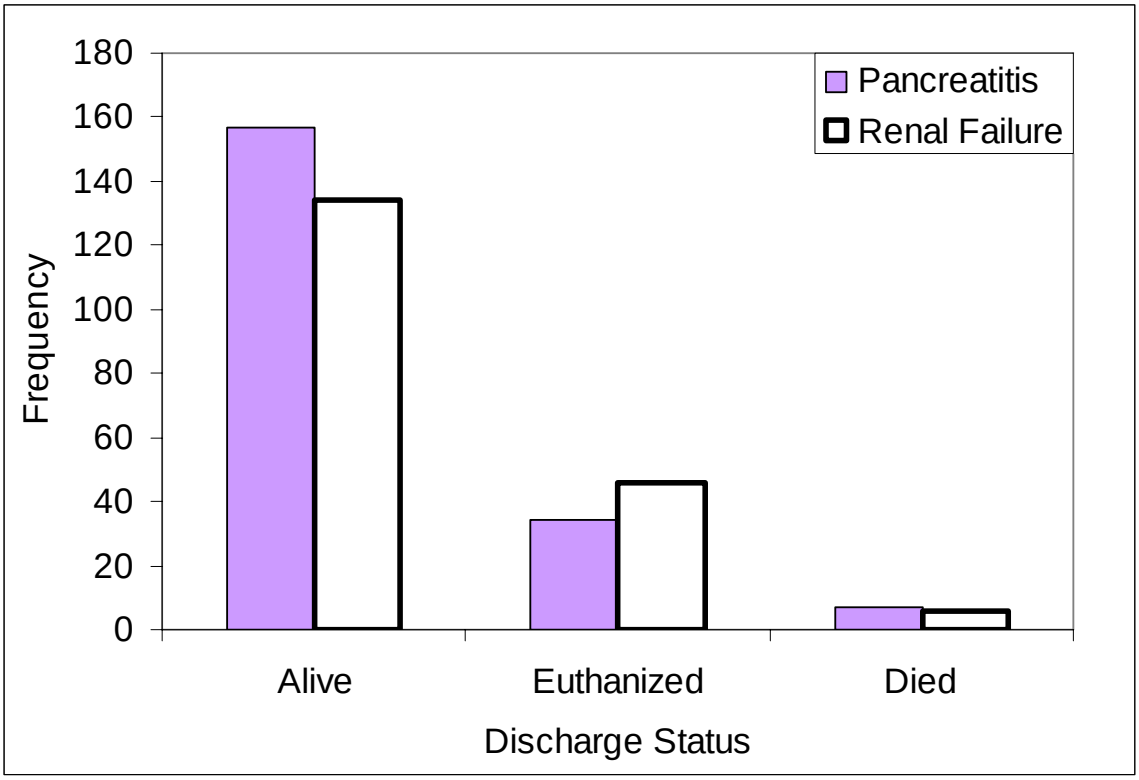

Figure A-7. Distribution of discharge status of the animal at the time of discharge for pancreatitis (cases) or renal failure (controls) patients.

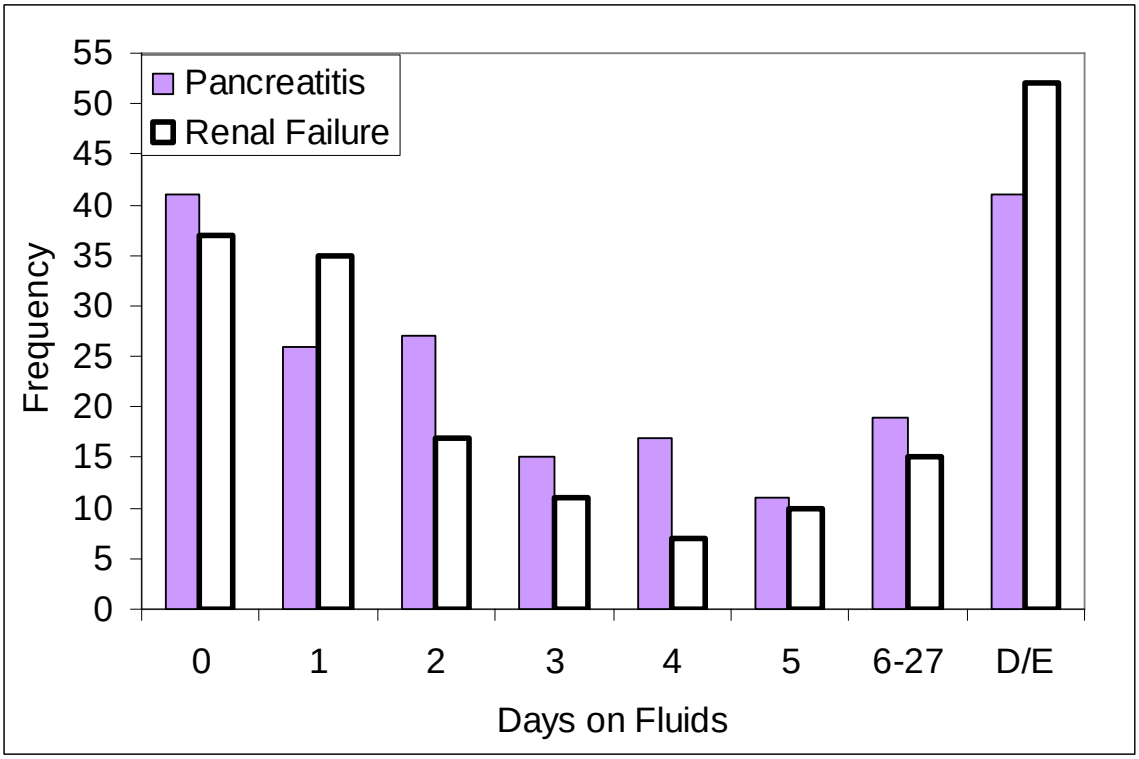

Figure A-8. Distribution of the number of days only patients that were discharged alive received intravenous fluids versus dogs that died or were euthanized (D/E) at the TAMU SAC for pancreatitis (cases) or renal failure (controls).

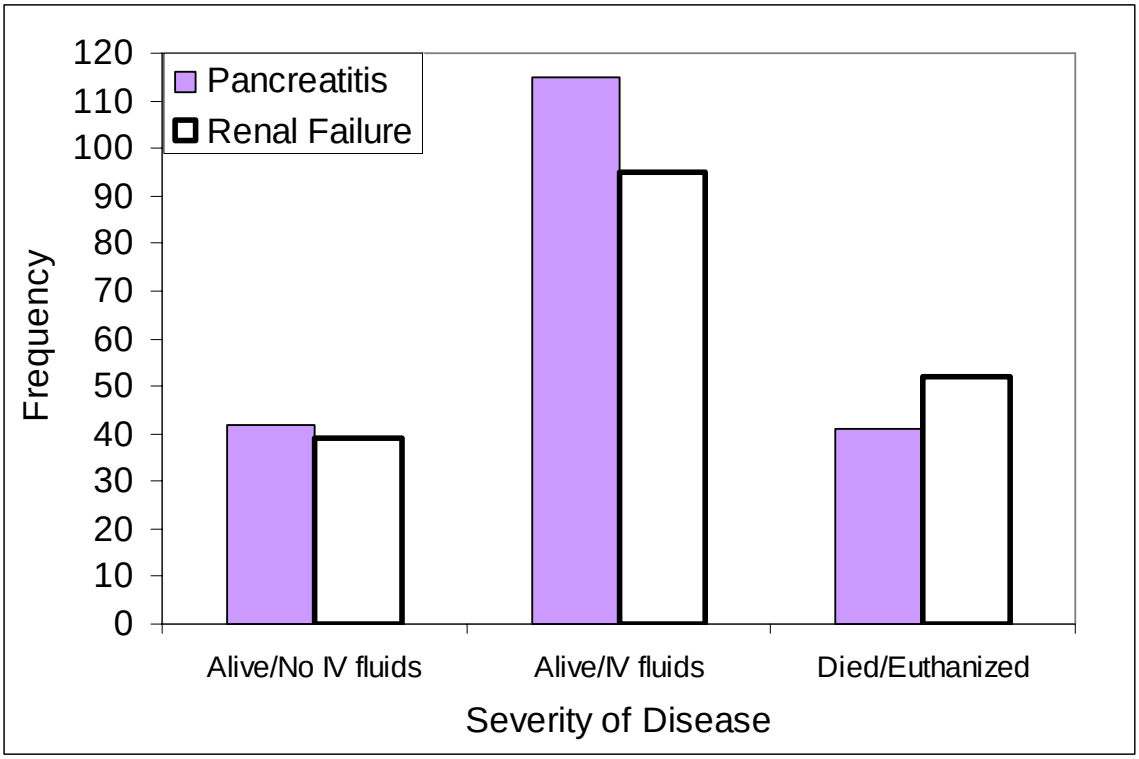

Figure A-9. Distribution of the measure of severity of disease for pancreatitis (cases) or renal failure (controls) patients.

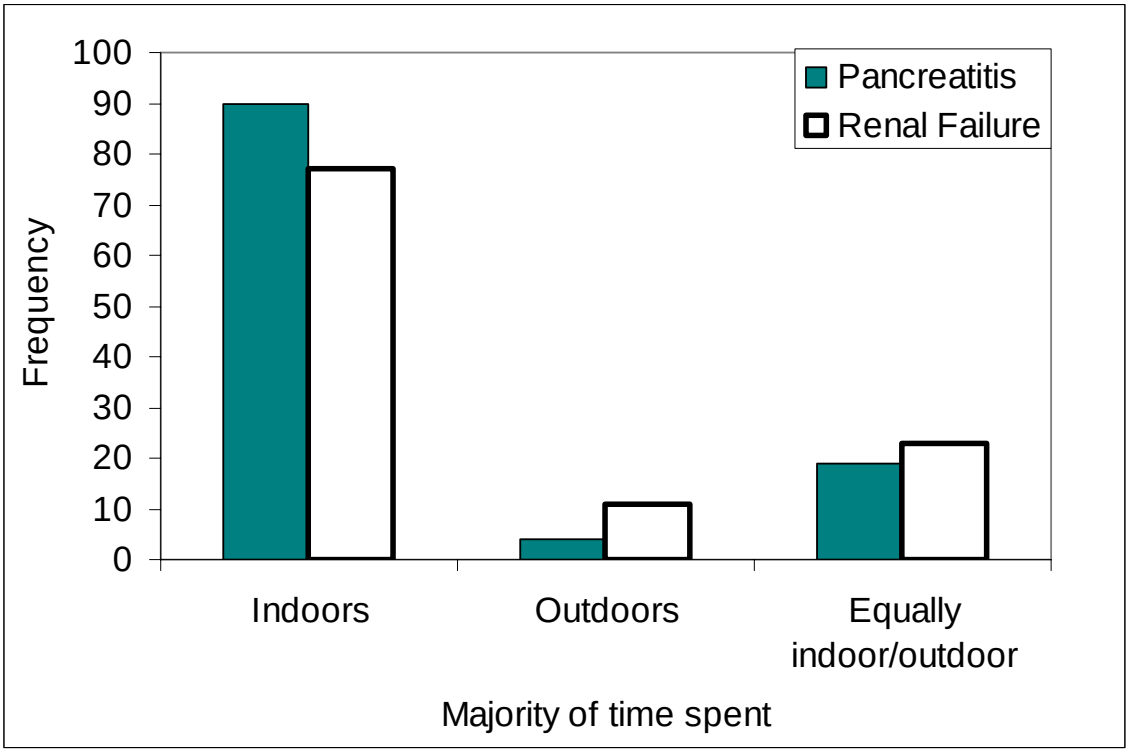

Figure A-10. Distribution of being kept indoors or outdoors for pancreatitis (cases) or renal failure (controls) patients.

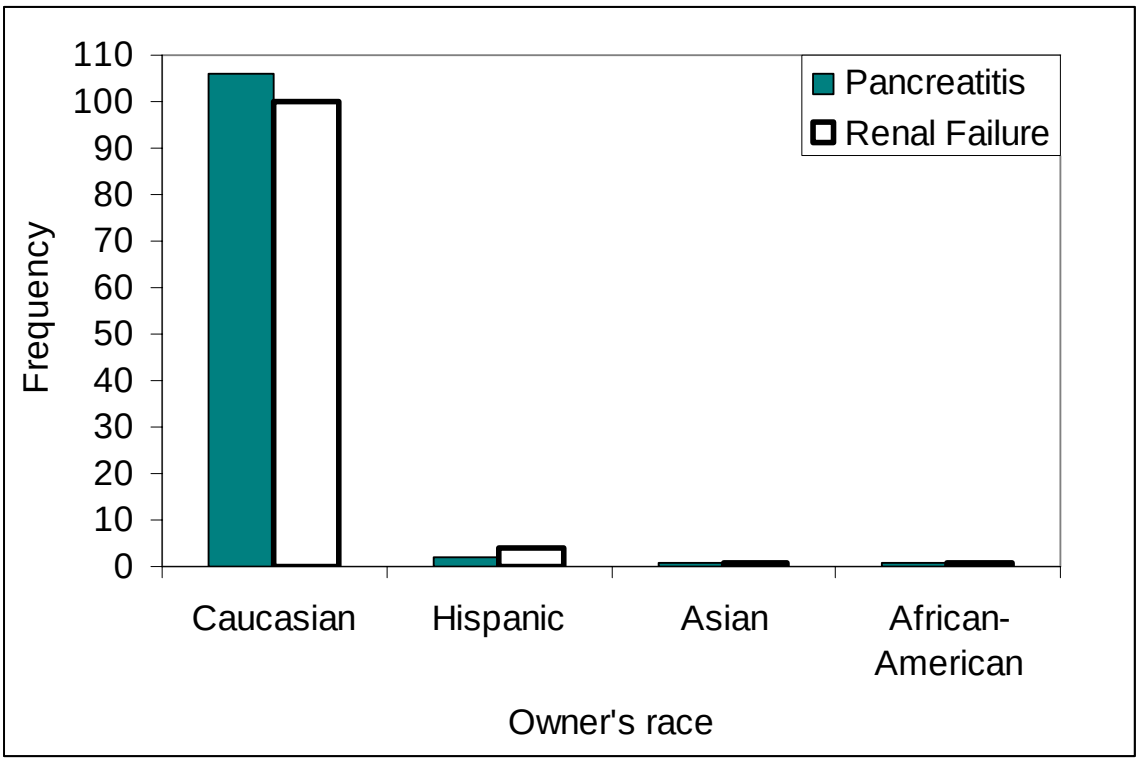

Figure A-11. Distribution of the owner's race for pancreatitis (cases) or renal failure (controls) patients.

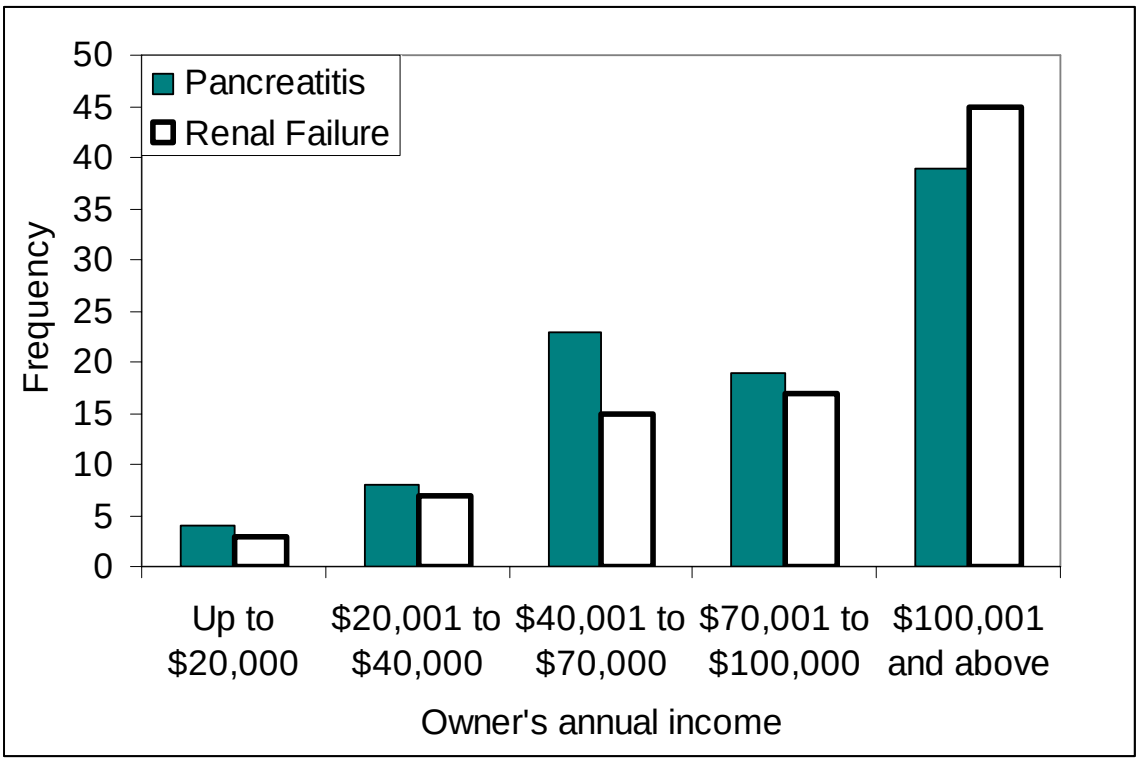

Figure A-12. Distribution of the owner's annual income for pancreatitis (cases) or renal failure (controls) patients.

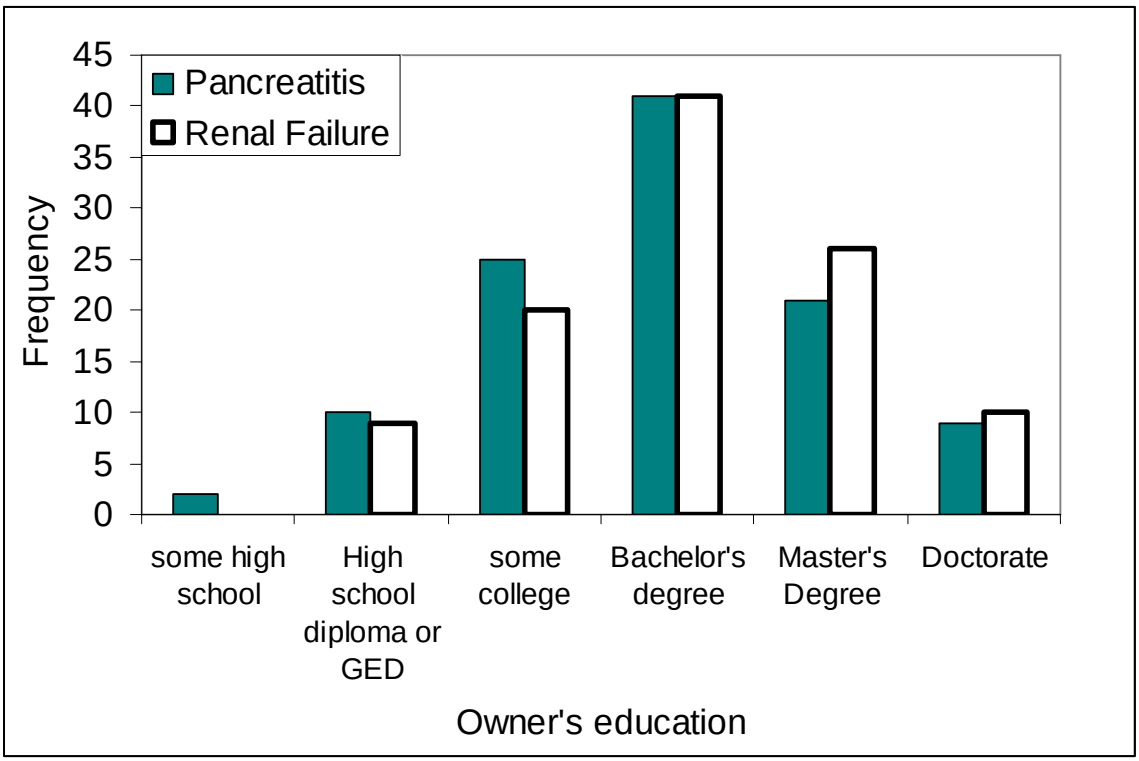

Figure A-13. Distribution of the owner's level of education for pancreatitis (cases) or renal failure (controls) patients.

Table A-41. Pearson's chi-square test for comparison of categorical variables with more than two categories between the case group and the the control group.

Pearson chi-square tests comparing case group to control group			
Variable	**chi-square**	**df**	**P value**
Sex and sexual status	19.627	3	0.0002
AKC breed groups	24.580	7	0.001
All breeds	23.877	6	0.001
Breed	16.656	5	0.005
Year of diagnosis	14.771	5	0.011
Body condition	9.099	2	0.011
Discharge status	3.323	2	0.190
Fluids	8.448	6	0.207
Severity	2.945	2	0.229
Housing	4.642	2	0.098
Owner's race	0.768	3	0.857
Owner's annual income	2.236	4	0.692
Owner's education	3.174	5	0.673

Table A-42. Descriptive statistics of the continuous variables for the telephone questionnaire responders. Data were collected from the medical record for the date of visit.

Telephone Questionnaire Responders					
Variable	**Mean**	**Median**	**Interquartile range**	**Standard deviation**	**Kolmogorov-Smirnov P value**
Age (years)	7.97	8.00	6.00	0.253	0.001
Weight (lbs)	36.95	26.60	41.00	1.822	0.000
Hospital stay (days)	3.4	2.0	5.0	0.26	0.00
IV fluids (days)	2.2	1.0	4.0	0.20	0.00
cPLI (µg/L)	363.21	351.60	374.40	33.196	0.200

Table A-43. Descriptive statistics of the continuous variables for the telephone questionnaire non-responders. Data were collected from the medical record for the date of visit.

Telephone Questionnaire Non-responders					
Variable	**Mean**	**Median**	**Interquartile range**	**Standard deviation**	**Kolmogorov-Smirnov P value**
Age (years)	6.98	7.00	7.00	0.348	0.004
Weight (lbs)	31.74	22.40	34.00	2.180	0.000
Hospital stay (days)	3.6	2.0	5.0	0.34	0.00
IV fluids (days)	2.1	1.3	3.0	0.19	0.00
cPLI (µg/L)	346.51	232.00	402.10	51.685	0.001*

*The Shapiro-Wilk P value is given because the number of data points was less than 50. This P value is based on 35 data points.

Table A-44. Mann-Whitney U test for equality of medians of the non-normally distributed, continuous variables between the telephone questionnaire responders and the non-responders. Data were collected from the medical record for the date of visit.

Mann-Whitney U test comparing responders to non-responders		
Variable	**Z**	**P value**
Age (years)	-2.397	0.17
Weight (lbs)	-1.988	0.047
Hospital stay (days)	-0.406	0.685
IV fluids (days)	-0.38	0.704
cPLI (µg/L)	-0.79	0.429

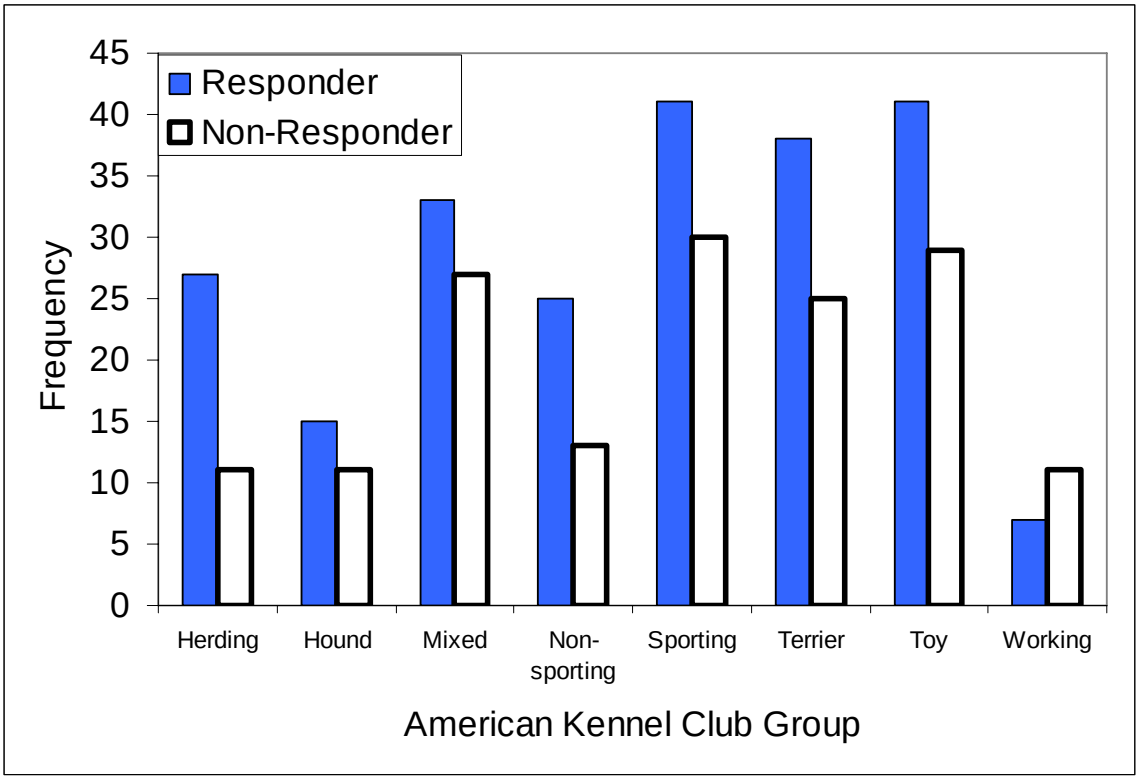

Figure A-14. Distribution of American Kennel Club breed groups for telephone questionnaire responders and non-responders.

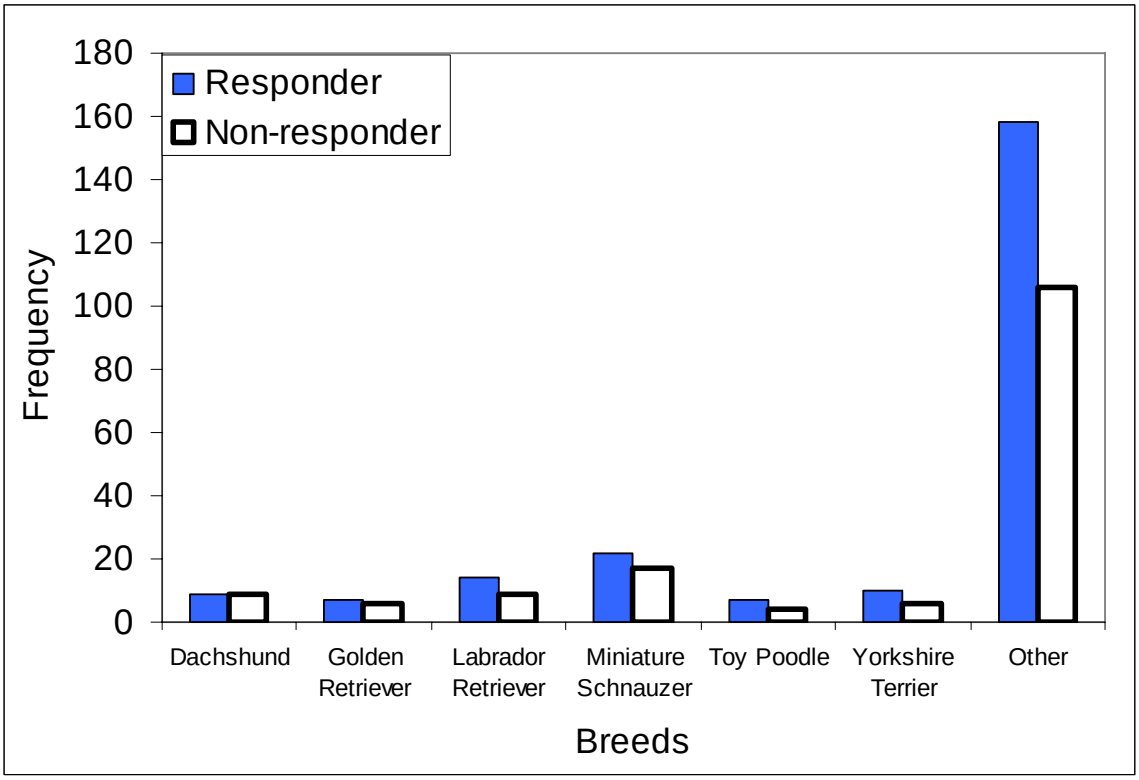

Figure A-15. Distribution of breeds with five or more dogs diagnosed with pancreatitis for telephone questionnaire responders and non-responders.

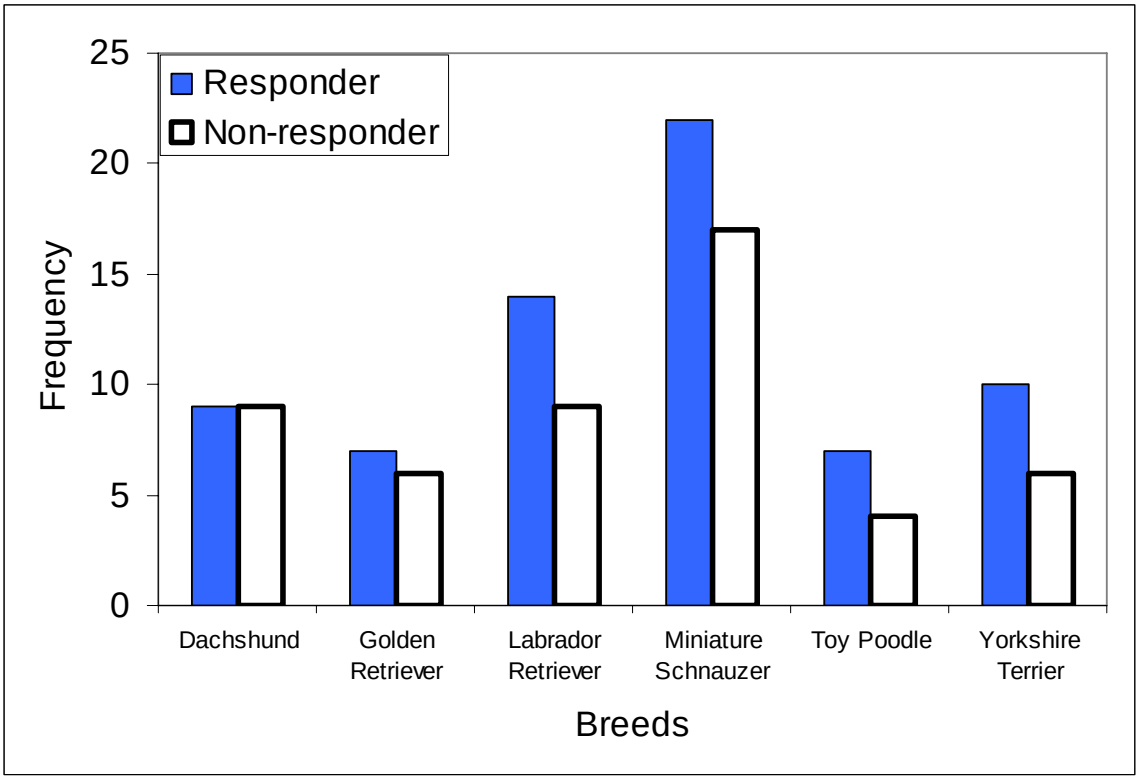

Figure A-16. Distribution of breeds with five or more dogs diagnosed with pancreatitis for telephone questionnaire responders and non-responders.

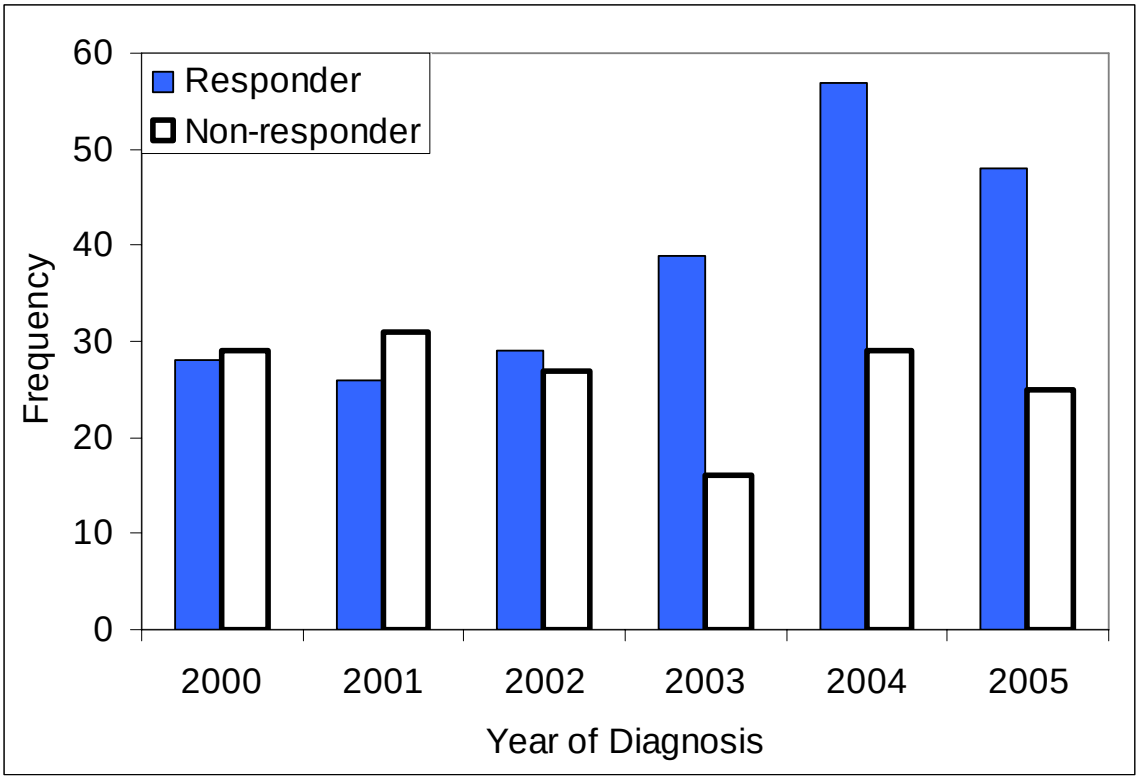

Figure A-17. Distribution of year of diagnosis for telephone questionnaire responders and non-responders.

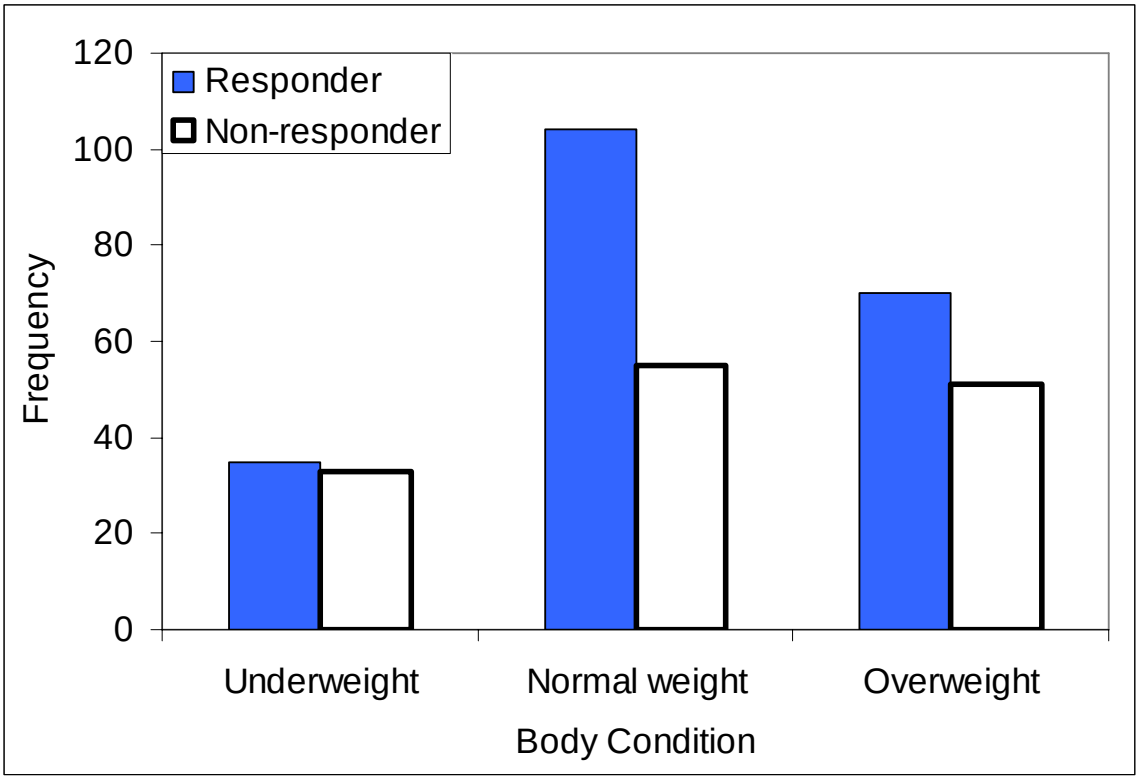

Figure A-18. Distribution of body condition when the dog presented at the hospital for telephone questionnaire responders and non-responders.

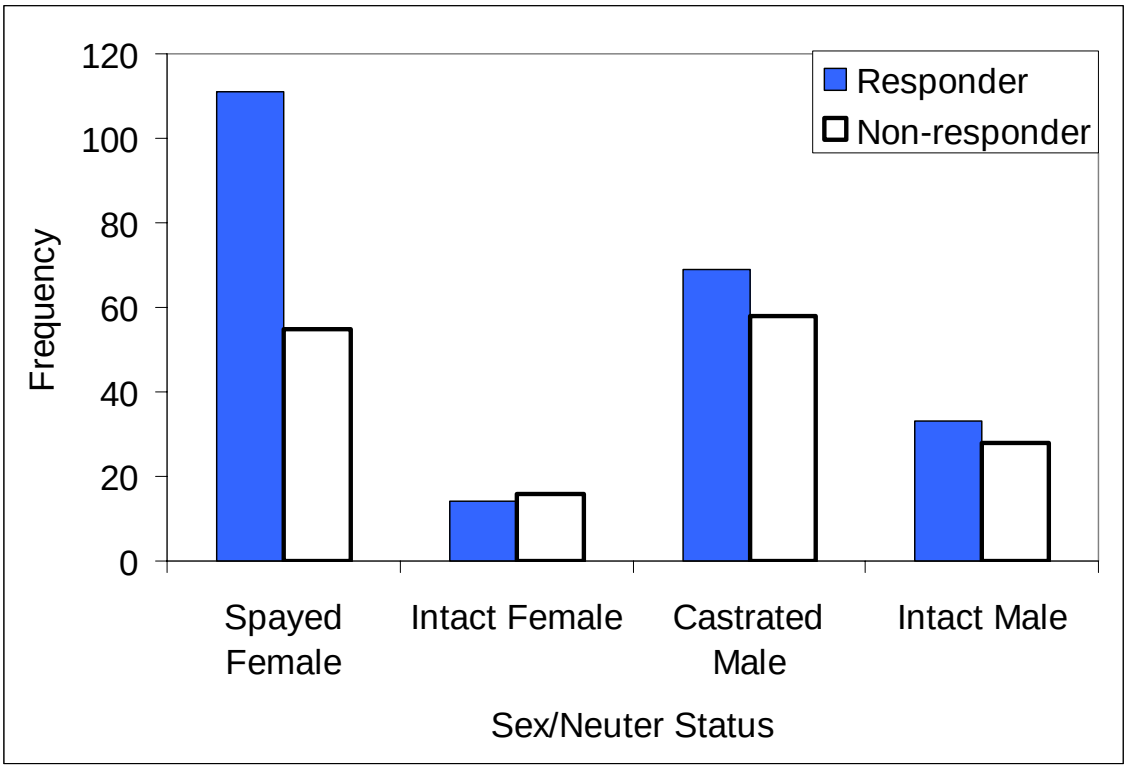

Figure A-19. Distribution of sex and sexual status for telephone questionnaire responders and non-responders.

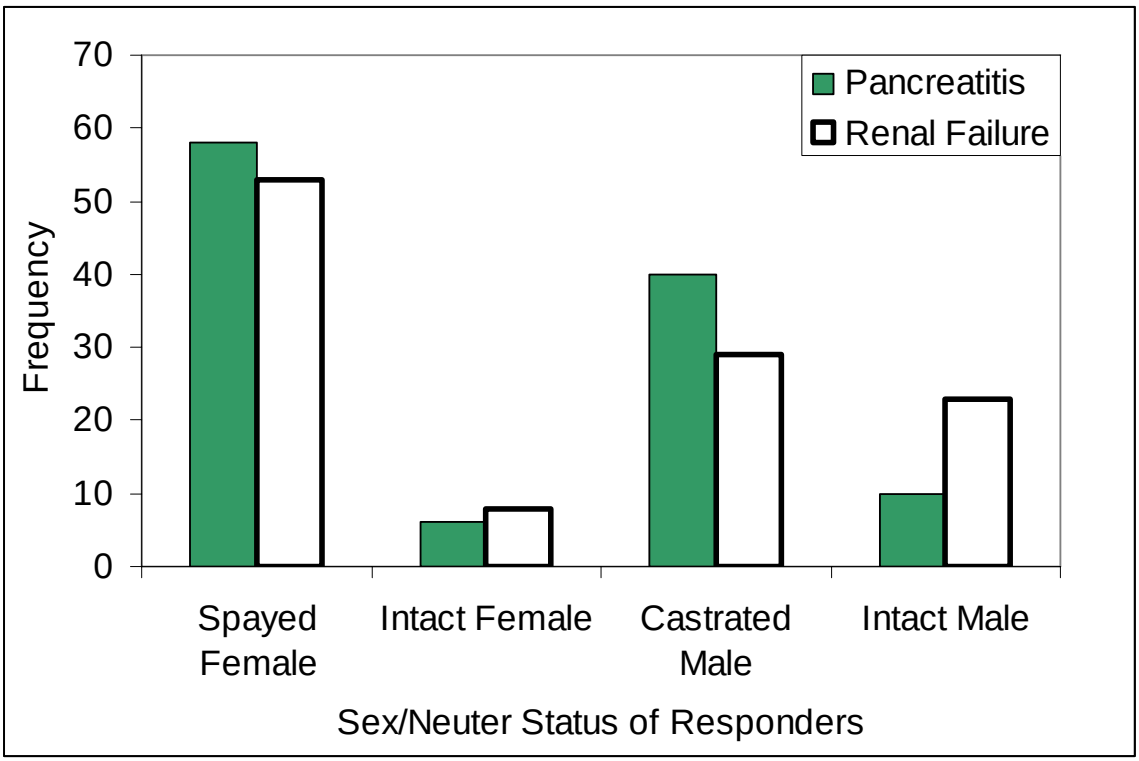

Figure A-20. Distribution of sex and sexual status of the telephone questionnaire responders for pancreatitis (cases) or renal failure (controls) patients.

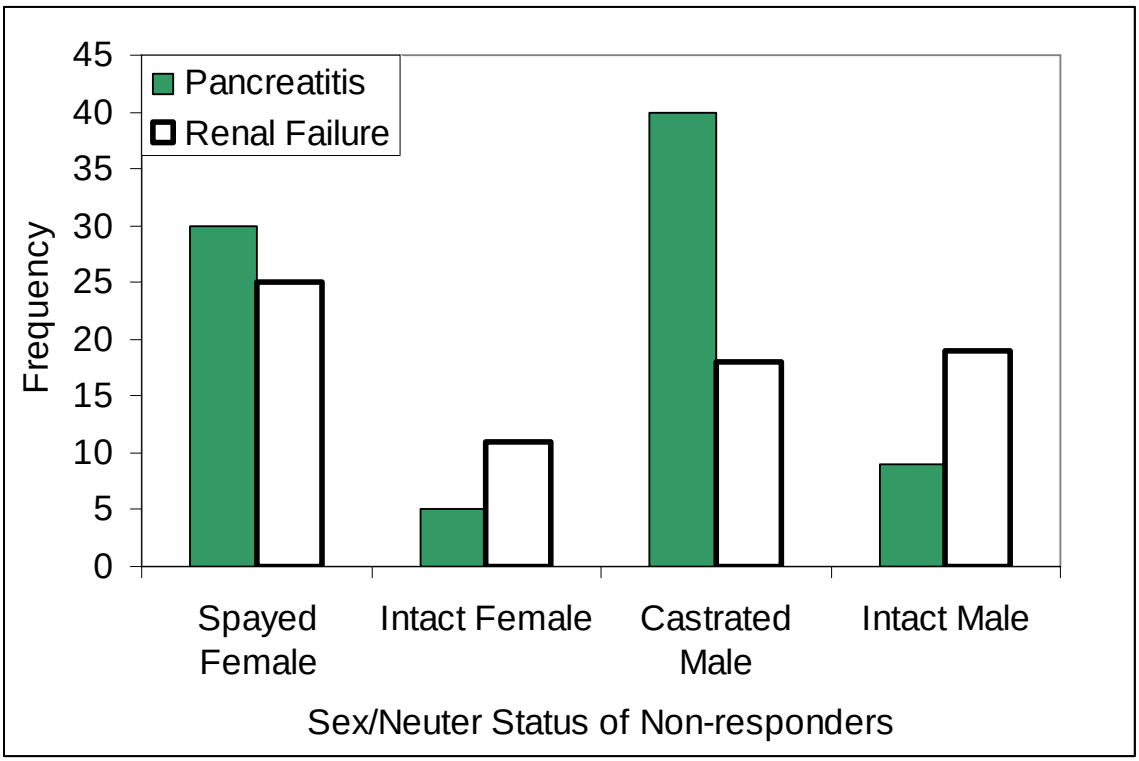

Figure A-21. Distribution of sex and sexual status of the telephone questionnaire non-responders for pancreatitis (cases) or renal failure (controls) patients.

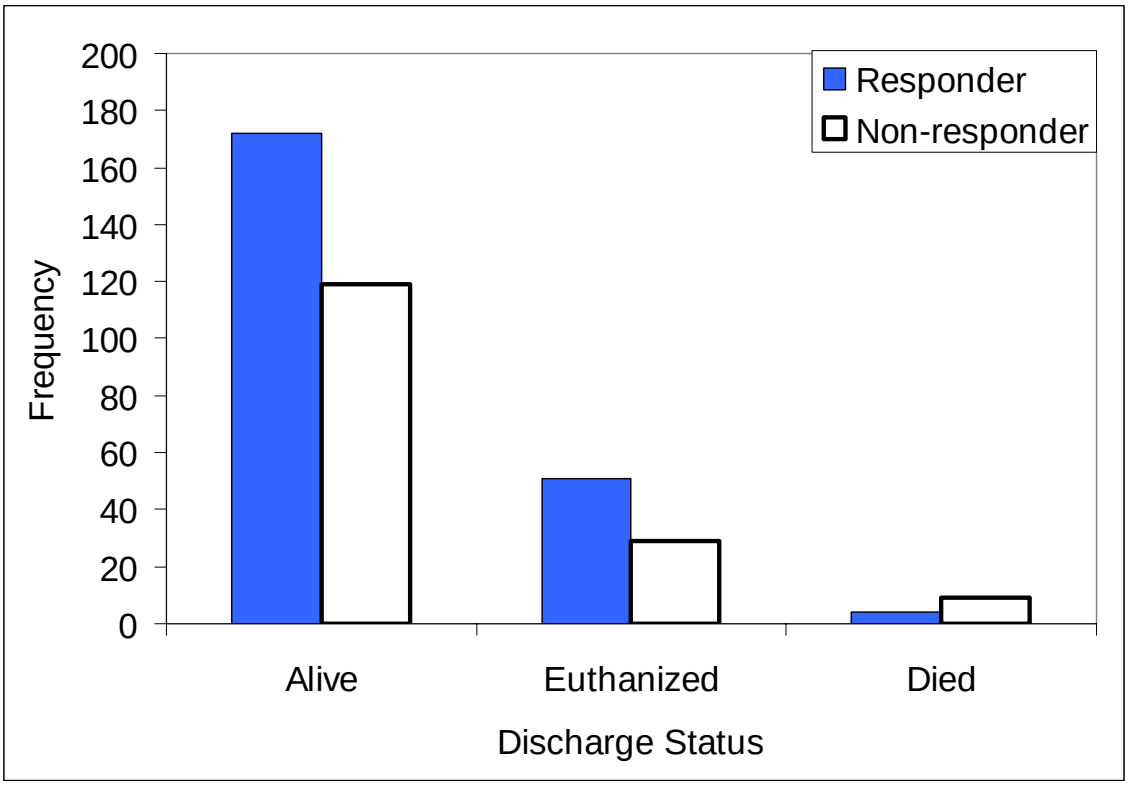

Figure A-22. Distribution of discharge status of the patient for telephone questionnaire responders and non-responders.

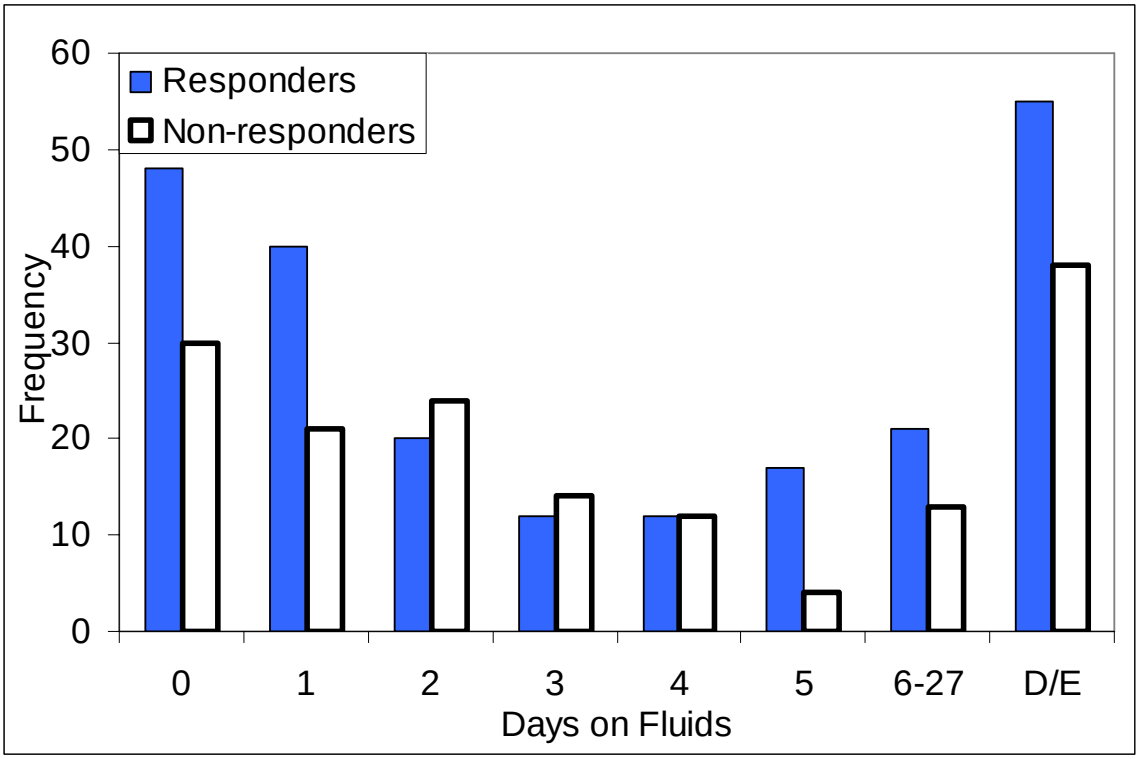

Figure A-23. Distribution of the number of days only patients that were discharged alive received intravenous fluids versus dogs that died or were euthanized (D/E) at the TAMU SAC for telephone questionnaire responders and non-responders.

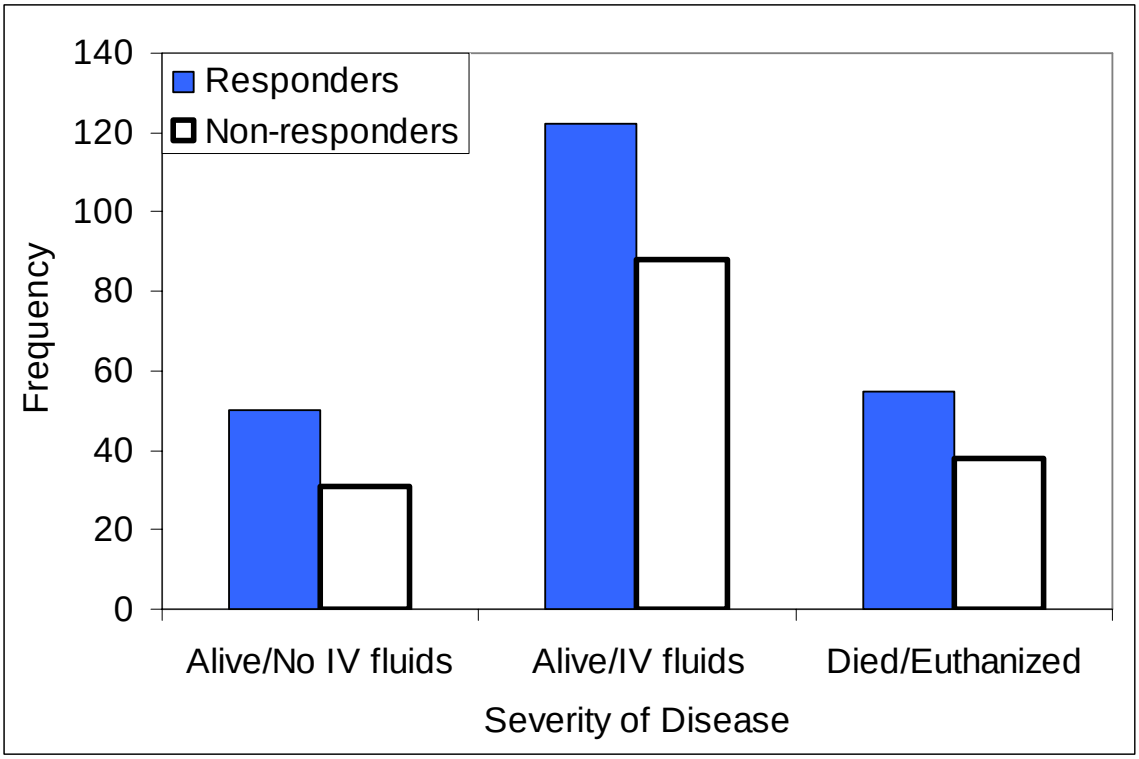

Figure A-24. Distribution of the measure of severity of disease for telephone questionnaire responders and non-responders.

Table A-45. Pearson's chi-square test for comparison of categorical variables with more than two categories between the telephone questionnaire responders and non-responders. Data were collected from the medical record for the date of visit.

Pearson chi-square tests comparing telephone questionnaire responders and non-responders			
Variable	**chi-square**	**df**	**P value**
AKC breed group	6.531	7	0.479
All breeds	1.143	6	0.980
Breed	0.944	5	0.967
Year of diagnosis	14.221	5	0.014
Body condition	4.234	2	0.120
Sex and sexual status	7.889	3	0.0480
Discharge status	5.033	2	0.081
Fluids	7.071	6	0.314
Severity	0.319	2	0.852

Table A-46. Pearson's chi-square test for comparison of sex and sexual status of dogs of telephone questionnaire responders and non-responders between the case group and control group. Data were collected from the medical record for the date of visit.

Pearson chi-square tests comparing case group to control group			
Variable	**chi-square**	**df**	**P value**
Sex and sexual status of dogs of responders	7.382	3	0.061
Sex and sexual status of dogs of non-responders	13.918	3	0.003

APPENDIX B

Version 1, 07/11/06

Information Sheet
Canine Health Survey

You have been asked to participate in a research project investigating common diseases in dogs. This study is the Master's thesis in Epidemiology for Kristina Lem, DVM. You were selected as a possible participant because you have taken one or more of your dogs to the Small Animal Clinic at Texas A&M University during the past six years. A total of 432 people will be asked to participate in this study. The purpose of this study is to identify risk factors that predispose dogs like yours to common and preventable diseases.

If you agree to be in this study, you will be asked to answer questions by phone concerning the history of your dog's health. These are the same types of questions that you would be asked about your dog during a normal veterinary visit. Your answers will be recorded on paper and entered into a computer database. There will not be any audio taping during the survey. This telephone survey will take 10 minutes, and you will not be contacted again for the purposes of this study. The risks associated with this study are minimal. The information collected from you during the survey is unlikely to cause stress. Any reactions to these questions are unlikely to be riskier than reactions to everyday occurrences. There are no direct benefits to you for participation in this survey beyond a sense of satisfaction for participation.

You will not receive any monetary or other form of compensation for participation in this survey.

This study is confidential. The records of this study will be kept private. No identifiers linking you to the study will be included in any sort of report that might be published. Research records will be stored securely and only Drs. Kristina Lem, Geoffrey Fosgate, Bo Norby, and Thomas Wehrly will have access to the records. Your decision whether or not to participate will not affect your current or future relations with Texas A&M University. If you decide to participate, you are free to refuse to answer any of the questions that may make you uncomfortable. You can withdraw at any time without your relations with the University, job, benefits, etc., being affected. You can contact Kristina Lem at 979-845-3240, kfoley@cvm.tamu.edu or Geoffrey Fosgate at 979-845-3203, gfosgate@cvm.tamu.edu with any questions about this study.

This research study has been reviewed by the Institutional Review Board – Human Subjects in Research, Texas A&M University. For research-related problems or questions regarding subject's rights, you can contact the Institutional Review Board through Ms. Angelia M. Raines, Director of Research Compliance, Office of the Vice President for Research at (979)458-4067, araines@vprmail.tamu.edu.

Please be sure you have read the above information, asked questions and received answers to your satisfaction. You will be given a copy of the information sheet for your records.

Signature of Investigator: _____ Date: _____

Letter to Owners

November 20, 2006

«AddressBlock»

«GreetingLine»

As you may know, our dogs can become ill despite our best efforts to keep them healthy. It can be quite frustrating when our options become limited to help them have a long and healthy life. I am writing this letter to inform you of a project investigating common diseases in dogs that we are beginning right now. We need your help for the collection of information concerning your dog's health. You have been contacted because you have taken one or more of your dogs to the Texas A&M Small Animal Clinic during the past 6 years.

An information sheet and a copy of the canine-health telephone survey are enclosed with this letter for your information. Specifically, we would like to have your help in filling out this survey over the telephone when I call you within the next couple of weeks.

Your required duties, should you participate in this voluntary survey, are as follows:

- Answer the questions in the survey to the best of your ability over the telephone when I call.

This collaborative research project involves Drs. Kristina Lem, Geoffrey Fosgate, and Bo Norby in the College of Veterinary Medicine and Dr. Thomas Wehrly in the Department of Statistics at Texas A&M. It would be greatly appreciated if you would take 10 minutes out of your busy schedule to help us out, when I call.

Thank you for your time and we look forward to your participation.

Sincerely,

Kristina Y. Lem, DVM

Telephone Script

Telephone Number: «Home_Phone» Alternate Number: «Mobile_Phone»
1st attempt:Date: _____ Time: _____ □Survey □Ans. Machine □No Contact
Notes: _____
2nd attempt:Date: _____ Time: _____ □Survey □Ans. Machine □No Contact
Notes: _____
3rd attempt:Date: _____ Time: _____ □Survey □Ans. Machine □No Contact
Notes: _____

Answering Machine Message: Hello, I would like to talk to you about your dog, «Patient». My name is Dr. Kristina Lem and I am calling from the Texas A&M College of Veterinary Medicine. I am conducting a short 10 minute survey of 432 participants about common diseases that affect dogs like yours. You have been chosen because you have taken one or more of your dogs to the Texas A&M Small Animal Clinic during the past 6 years. I will be calling again to ask you to participate. If you have any questions about any aspect of this study you may call me at 979-845-3240. Thank you.

Telephone Survey: Hello, I would like to talk to you about your dog, «Patient». My name is Dr. Kristina Lem and I am calling from the Texas A&M College of Veterinary Medicine. May I speak with the primary owner of «Patient»? I am conducting a 10 minute survey of 432 participants, concerning common diseases that affect dogs, like yours. You have been chosen because you have taken one or more of your dogs to the Texas A&M Small Animal Clinic during the past 6 years.

Will you help us by answering some questions about your dog's health? YES NO

[If yes, continue with survey]
[If no] Is there a better time when I can call you back? _____

Did you receive the information sheet that I sent to you in the mail? YES NO

[If yes] Do you have any questions? [Answer questions and skip to the survey questions]
[If no, read the following introduction]

Before we get started, I have a statement to read to you regarding your rights as a participant in this voluntary survey.

First of all, thank you for choosing to participate. You may refuse to answer any individual question and you have the right to withdraw your participation at any time, without penalty. This telephone survey will be maintained confidentially by the researchers and only presented in group form. The information collected from you during this survey is unlikely to cause stress. It is expected that any reactions to the questions are unlikely to be riskier than reactions to everyday occurrences.

I hope that you will gain satisfaction from the fact that your participation in this program will help to improve our knowledge of canine diseases and potentially help dogs. If you have any questions about your participation in this study you may call me, Kristina Lem, at (979)845-3240.

This research study has been reviewed by the Institutional Review Board – Human Subjects in Research, Texas A&M University. For research-related problems or questions regarding subjects' rights, you can contact the Institutional Review Board through Ms. Angelia M. Raines, Director of Research Compliance, Office of the Vice President for Research at (979)458-4067.

Please answer the following questions to the best of your ability.

1. Do you or anyone in your household have, or have you had a dog by the name of «Patient»?
    a. yes; [continue with questionnaire]
    b. no; "thank you for your time" [and end the call]

2. How old is «Patient»?
    a. _____years; _____months
    b. Deceased
    [If deceased] I am very sorry to hear that. Thank you again for agreeing to answer some questions about «Patient».

3. Our records show that you brought «Patient» to the Texas A&M Small Animal Clinic on «Admit». Is this correct?

YES NO

[If yes] What was the primary reason for that visit?

_____

_____

_____

[If no] When did you take «Patient» to the TAMU Small Animal Clinic?

_____

The remainder of the questions are concerning the time around that visit on «Admit». For that reason, the questions will be asked in the past tense.

4. Could you please tell me the following information about «Patient» at the time of that visit?
    a. breed?_____
    b. gender? MALE FEMALE
    c. Was «Patient» spayed or neutered at that time? YES NO
    d. How much did he/she weigh? _____lbs

5. At the time of the visit, where did «Patient» spend the majority of his/her time at home? [read off the choices]
    a. Inside? _____
    b. Outside? _____
    c. Or both equally? _____

6. Were you referred to TAMU by another veterinarian? YES NO
    a. [If yes] Who referred you to TAMU? [read off the choices]
        i. Your regular veterinarian?
        ii. Another referral hospital?
        iii. Someone else?

        _____
    b. [If no] Did you come to TAMU without a referral? YES NO

7. What symptoms was «Patient» showing that prompted you to take him/her to the TAMU Small Animal Clinic?

    _____
    _____
    _____
    _____

8. At this time, was «Patient»
    a. Current on his/her vaccinations? YES NO
    b. Was he/she on monthly heartworm preventive? YES NO
    c. Was he/she taking any prescription medications? YES NO

9. Did «Patient» have any prior
    a. illnesses YES NO
    [If yes] What were they and when did they occur?

    _____
    _____
    _____
    _____

    b. Did he/she have any prior surgical operations? YES NO
    [If yes] What were they and when did they occur?

    _____
    _____
    _____
    _____

    c. Did he/she have any prior traumatic injuries? YES NO
    [If yes] What were they and when did they occur?

    _____
    _____
    _____
    _____

10. Did you have any other pets in the household at that time? YES NO
[If yes] What were they?

_____
_____
_____

11. During the week just before that visit
    a. What type of food and how much were you feeding «Patient»?

    _____
    _____

    b. During that week, did «Patient» eat anything out of the ordinary?
    YES NO
    [If yes] What was it?

    _____
    _____

    c. During that week, did «Patient» receive any table scraps?
    YES NO
    [If yes] What did he/she receive?

    _____
    _____

    d. Did «Patient» normally receive table scraps?
    YES NO
    [If yes] What did he/she normally receive?

    _____
    _____

    e. During that week, did «Patient» eat anything out of the trash?
    YES NO
    [If yes] What did he/she eat out of the trash?

    _____
    _____

    f. During that week, did you have a large family meal or get together with food?
    YES NO
    [If yes] Was «Patient» at the get together? YES NO

    _____
    _____

12. What was «Patient» diagnosed with during the visit to the TAMU Small Animal Clinic on «Admit»?

    _____
    _____
    _____

That completes the questions about «Patient». For classification purposes, I have some questions about the primary owner of «Patient» at the time of the visit mentioned above. Identification of any person will not be attached to these questions in any form. You may decline to answer these questions. May we continue?
YES NO

[If yes, continue with questions]
[If no, skip to the end]

13. Was the primary owner MALE or FEMALE?

14. What year was he/she born?

    _____

15. What was his/her race?

    _____

16. What was the approximate total household income for that year? [Let them give you a number, then circle the correct category]
    a. Under $20,000
    b. $20,001 to $40,000
    c. $40,001 to $70,000
    d. $70,001 to $100,000
    e. $100,001 and above

17. What was the highest level of education completed by the primary owner at the time of the visit? [Let them respond, then circle the correct category]
    a. Some high school
    b. High school diploma or GED
    c. Some college
    d. Bachelor's degree
    e. Master's degree
    f. Doctorate (PhD, MD, DVM, etc)

That completes the survey. Do you have any questions for me? [Answer any questions]
Thank you for your time. [Hang up the phone]

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